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APPLICATION NUMBER: *10/413,022*
FILING DATE: *April 14, 2003*

PRIORITY DOCUMENT
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FEE RECORD SHEET

04/16/2003 HLE333 00000007 500552 10413022

01 FC:1001		750.00 OP
02 FC:1201		3864.00 OP
03 FC:1202	54.00 CH	1872.00 OP
04 FC:1203	280.00 CH	

PTO-1556
(5/87)

*U.S. Government Printing Office: 2001 — 481-697/59173

Express Mail Label No. EV 175 242 958 US

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 478.1045US

Total Pages in this Submission 103

TO THE ASSISTANT COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

COMPOSITION, DEVICE, AND METHOD FOR TREATING SEXUAL DYSFUNCTION VIA INHALATION

and invented by:

John Nicolas Staniforth, David Morton, Michael Tobyn, Stephen Eason, Quentin Harmer, David Ganderton

If a CONTINUATION APPLICATION, *check appropriate box and supply the requisite information:*

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: ______

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Enclosed are:

Application Elements

1. ☒ Filing fee as calculated and transmitted as described below
2. ☒ Specification having 74 pages and including the following:
   - a. ☐ Descriptive Title of the Invention
   - b. ☒ Cross References to Related Applications *(if applicable)*
   - c. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
   - d. ☐ Reference to Sequence Listing, a Table, or a Computer Program Listing Appendix
   - e. ☒ Background of the Invention
   - f. ☒ Brief Summary of the Invention
   - g. ☒ Brief Description of the Drawings *(if filed)*
   - h. ☒ Detailed Description
   - i. ☒ Claim(s) as Classified Below
   - j. ☒ Abstract of the Disclosure

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)
(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
478.1045US

Total Pages in this Submission
103

Application Elements (Continued)

3. ☒ Drawing(s) *(when necessary as prescribed by 35 USC 113)*
   a. ☒ Formal Number of Sheets 22
   b. ☐ Informal Number of Sheets _____
4. ☒ Oath or Declaration
   a. ☐ Newly executed *(original or copy)* ☒ Unexecuted
   b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
   c. ☒ With Power of Attorney ☐ Without Power of Attorney
   d. ☐ *DELETION OF INVENTOR(S)*
   Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference *(usable if Box 4b is checked)*
   The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ CD ROM or CD-R in duplicate, large table or Computer Program (Appendix)
7. ☐ Application Data Sheet (See 37 CFR 1.76)
8. ☐ Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all must be included)*
   a. ☐ Computer Readable Form (CRF)
   b. ☐ Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ Paper
   c. ☐ Statement(s) Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

9. ☐ Assignment Papers *(cover sheet & document(s))*
10. ☐ 37 CFR 3.73(B) Statement *(when there is an assignee)*
11. ☐ English Translation Document *(if applicable)*
12. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations
13. ☐ Preliminary Amendment
14. ☒ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
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UTILITY PATENT APPLICATION TRANSMITTAL (Large Entity) *(Only for new nonprovisional applications under 37 CFR 1.53(b))*	Docket No. 478.1045US
	Total Pages in this Submission 103

Accompanying Application Parts (Continued)

17. ☐ Additional Enclosures *(please identify below):*

Request That Application Not Be Published Pursuant To 35 U.S.C. 122(b)(2)

18. ☐ Pursuant to 35 U.S.C. 122(b)(2), Applicant hereby requests that this patent application not be published pursuant to 35 U.S.C. 122(b)(1). Applicant hereby certifies that the invention disclosed in this application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication of applications 18 months after filing of the application.

Warning

An applicant who makes a request not to publish, but who subsequently files in a foreign country or under a multilateral international agreement specified in 35 U.S.C. 122(b)(2)(B)(i), must notify the Director of such filing not later than 45 days after the date of the filing of such foreign or international application. A failure of the applicant to provide such notice within the prescribed period shall result in the application being regarded as abandoned, unless it is shown to the satisfaction of the Director that the delay in submitting the notice was unintentional.

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
478.1045US

Total Pages in this Submission
103

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra		Rate	Fee
Total Claims	124	- 20 =	104	x	$18.00	$1,872.00
Indep. Claims	49	- 3 =	46	x	$84.00	$3,864.00
Multiple Dependent Claims (check if applicable) ☐						$0.00
					BASIC FEE	$750.00
OTHER FEE *(specify purpose)*						$0.00
					TOTAL FILING FEE	$6,486.00

☒ A check in the amount of **$6,486.00** to cover the filing fee is enclosed.

☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. **50-0552** as described below. A duplicate copy of this sheet is enclosed.

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- ☒ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Signature

Dated: **April 14, 2003**

Cary S. Kappel, Reg. No. 36,561
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485 Seventh Avenue, 14th Floor
New York, New York 10018

23280
PATENT TRADEMARK OFFICE

cc:

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): **John NICOLAS, et al.**			Docket No. **478.1045US**
Serial No. **To Be Assigned**	Filing Date **Herewith**	Examiner **To Be Assigned**	Group Art Unit **To Be Assigned**

Invention: **COMPOSITION, DEVICE, AND METHOD FOR TREATING SEXUAL DYSFUNCTION VIA INHALATION**

I hereby certify that the following correspondence:

New Utility Patent Appication and Accompanying Documents.

(Identify type of correspondence)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231 on

April 14, 2003
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Kareem Stevens
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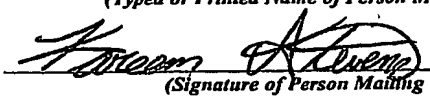

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DDK Docket No. 478.1045

Composition, Device, And Method For Treating Sexual Dysfunction Via Inhalation

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DDK Docket No. 478.1045

Composition, Device, And Method For Treating Sexual Dysfunction Via Inhalation

Background of the Invention

[0001] The term "erectile dysfunction" has been defined by the National Institutes of Health as the inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse. See J. Am. Med. Assoc., 270(1):83-90 (1993). Because adequate arterial blood supply is critical for erection, any disorder that impairs blood flow may be implicated in the etiology of erectile failure. Erectile dysfunction affects millions of men and, although generally regarded as a benign disorder, has a profound impact on their quality of life. It is recognized, however, that in many men psychological desire, orgasmic capacity, and ejaculatory capacity are intact even in the presence of erectile dysfunction.

[0002] Etiological factors for erectile disorders have been categorized as psychogenic or organic in origin. Organic factors include those of a neurogenic origin and those of a vasculogenic origin. Neurogenic factors include, for example, lesions of the somatic nervous pathways which may impair reflexogenic erections and interrupt tactile sensations needed to maintain erections, and spinal cord lesions which, depending upon their location and severity, may produce varying degrees of erectile failure.

[0003] Psychogenic factors for erectile dysfunction include such processes as depression, anxiety, and relationship problems which can impair erectile functioning by reducing erotic focus or otherwise reducing awareness of sensory experience. This may lead to an inability to initiate or maintain an erection.

[0004] Vasculogenic risk factors include factors which affect blood flow and include cigarette smoking, diabetes mellitus, hypertension, alcohol, vascular disease, high levels of serum cholesterol, low levels of high-density lipoprotein (HDL), and other

chronic disease conditions such as arthritis. The Massachusetts Male Aging Study (MMAS, as reported by H. A. Feldman, et al., J. Urol., 151: 54-61 (1994) found, for example, that the age-adjusted probability of complete erectile dysfunction was three times greater in subjects reporting treated diabetes than in those without diabetes. While there is some disagreement as to which of the many aspects of diabetes is the direct cause of erectile dysfunction, vascular disease is most frequently cited.

[0005] The MMAS also found a significant correlation between erectile dysfunction and heart disease with two of its associated risk factors, hypertension and low serum high density lipoprotein (HDL). It has been reported that 8-10% of all untreated hypertensive patients are impotent at the time they are diagnosed with hypertension. The association of erectile dysfunction with vascular disease in the literature is strong, with impairments in the hemodynamics of erection demonstrated in patients with myocardial infarction, coronary bypass surgery, cerebrovascular accidents, and peripheral vascular disease. It also found cigarette smoking to be an independent risk factor for vasculogenic erectile dysfunction, with cigarette smoking found to exacerbate the risk of erectile dysfunction associated with cardiovascular diseases.

[0006] As described in U.S. Patent Nos. 5,770,606 and 6,291,471, it is known to treat both psychogenic and organic erectile dysfunction in males with the opioid apomorphine. Apomorphine is a derivative of morphine, and was first evaluated for use as a pharmacologic agent as an emetic in 1869. In the first half of the 20th century, apomorphine was used as a sedative for psychiatric disturbances and as a behavior-altering agent for alcoholics and addicts. By 1967, the dopaminergic effects of apomorphine were realized, and the compound underwent intensive evaluation for the treatment of Parkinsonism. Since that time, apomorphine has been classified as a selective dopamine receptor agonist that stimulates the central nervous system producing an arousal response manifested by yawning and penile erection in animals and man.

[0007] WO 01/74358 purports to describe a method for treatment of male erectile dysfunction using an inhaled apomophine formulation. The formulations exemplified therein comprise a solution of apomorphine and sodium metabisulfite in water, which are said to have been introduced directly into the lungs of a dog via the trachea.

[0008] U.S. Patent No. 6,193,992 purports to describe a method of ameliorating sexual dysfunction in a human female which comprises administering to said human female apomorphine in an amount sufficient to increase intraclitoral blood flow and vaginal wall blood flow on stimulation of said female but less than the amount that induces substantial nausea

Summary of the Invention

[0009] In one aspect, the present invention is directed to methods for treating sexual dysfunction via inhalation therapy.

[0010] In accordance with one such embodiment of the present invention, a method for treating sexual dysfunction via inhalation is provided which comprises inhaling a dose of a powder composition, the powder composition comprising apomorphine or pharmaceutically acceptable salts thereof. Preferably, the powder composition further includes a carrier material, the carrier material has an average particle size of from about 40 to about 70 microns, and at least 90 percent of said apomorphine has a particle size of 5 microns or less.

[0011] In accordance with another embodiment of the present invention, a method for treating sexual dysfunction via inhalation is provided which comprises inhaling a dose of a powder composition, the dose of the powder composition comprising from about 100 micrograms to about 2000 micrograms of apomorphine or pharmaceutically acceptable salts thereof. Preferably, the dose comprises from about 100 micrograms to about 1600 micrograms of said apomorphine, more preferably, about 100 micrograms

to about 1000 micrograms of said apomorphine, and most preferably, about 100 micrograms to about 800 micrograms of said apomorphine.

[0012] In accordance with another embodiment of the present invention, a method for treating sexual dysfunction via inhalation is provided which comprises inhaling a dose of a powder composition, the powder composition comprising apomorphine or pharmaceutically acceptable salts thereof and a carrier material, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less.

[0013] In another aspect, the present invention is directed to unit doses of apomorphine.

[0014] In accordance with one such embodiment of the present invention, a dose is provided which comprises a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof.

[0015] In accordance with another embodiment of the present invention, a dose is provided which comprises a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less.

[0016] In accordance with another embodiment of the present invention, a drug loaded blister is provided which comprises a base having a cavity formed therein, the cavity containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof, the cavity having an opening which is sealed by a rupturable covering.

[0017] In accordance with another embodiment of the present invention, a drug loaded blister is provided which comprises a base having a cavity formed therein, the cavity containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less, the enclosure having an open end, the cavity having an opening which is sealed by a rupturable covering.

[0018] In the above referenced embodiments, the doses and/or drug loaded blisters preferably include from 1 to 5 milligrams of powder composition, wherein apomorphine or its pharmaceutically acceptable salts comprise from about 3 % to about 80 %, preferably from about 5% to about 50%, and most preferably from about 5% to about 30% of the powder composition.

[0019] In another aspect, the present invention is directed to methods for producing an inhalable aerosol of a powdered apomorphine composition.

[0020] In accordance with one such embodiment, the method comprises entraining a powdered composition in a gas flow upstream from an inlet port of a vortex chamber having a substantially circular cross-section. In this regard, in certain variants of this embodiment, the powder composition may include from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof and a carrier material. In other variants of this embodiment, the powder composition may include a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material has an average particle size of from about 40 to about 70 microns, and at least 90 percent of said apomorphine has a particle size of 5 microns or less. In any event, the method further comprises directing the gas flow through the inlet port into the vortex chamber in a tangential direction; directing the gas flow through the vortex chamber so as to aerosolise the powder composition; and directing the gas flow

with the powder composition out of the vortex chamber in an axial direction through an exit port, wherein a velocity of the gas flow at a distance of 300 mm outside of the exit port is less than a velocity of the gas flow at the inlet port.

[0021] In accordance with another embodiment of the present invention, the method comprises entraining a powdered composition including agglomerated particles in a gas flow upstream from an inlet port of a vortex chamber. In certain variants of this embodiment, the agglomerated particles include from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof and a carrier material. In other variants of this embodiment, the agglomerated particles include a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material has an average particle size of from about 40 to about 70 microns, and at least 90 percent of said apomorphine has a particle size of 5 microns or less. In either case, the method further comprises directing the gas flow through the inlet port into the vortex chamber; depositing the agglomerated particles onto one or more walls of the vortex chamber; applying, via the gas flow through the vortex chamber, a shear to the deposited agglomerated particles to deagglomerate said particles, and directing the gas flow, including the deagglomerated particles, out of the vortex chamber, wherein a velocity of the gas flow at a distance of 300 mm outside of the exit port is less than a velocity of the gas flow at the inlet port.

[0022] In accordance with another embodiment of the present invention, the method comprises entraining agglomerated particles in a gas flow. The agglomerated particles include a carrier material having an average particle size of from about 40 microns to about 70 microns and from about 100 to about 800 micrograms apomorphine or a pharmaceutically acceptable salt thereof. Preferably, at least 90% of said apomorphine has a particle size of 5 microns or less. The method further comprises depositing the agglomerated particles onto one or more surfaces; and applying, via the gas flow, a shear to the deposited agglomerated particles to deagglomerate said particles.

[0023] In accordance with another embodiment of the present invention, the method comprises generating an air flow through an inlet port of a chamber, the air flow having entrained therein a composition. In certain variants of this embodiment, the composition comprises from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof and a carrier material. In other variants of this embodiment, the composition includes a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material has an average particle size of from about 40 to about 70 microns, and at least 90 percent of said apomorphine has a particle size of 5 microns or less. The method further comprises directing the air flow through the chamber. The chamber has an axis and a wall curved about the axis and the air flow rotates about the axis. The method further directs the air flow through an exit port of the chamber, wherein a direction of the air flow through the inlet port is tangential to the wall, and a direction of the air flow through the exit port is parallel to the axis, and wherein a cross-sectional area of the air flow through the chamber is in a plane normal to the air flow and decreases with increasing distance from the inlet port.

[0024] In other aspects, the present invention is directed to inhalers for producing an inhalable aerosol of a powdered apomorphine composition.

[0025] In accordance with these embodiments, an inhaler for producing an inhalable aerosol of a powdered apomorphine composition comprises: an aerosolising device including a substantially tangential inlet port and a substantially axial exit port, one or more sealed blisters containing apomorphine or a pharmaceutically acceptable salt thereof, and an input for removably receiving one of the blisters. The inhaler, upon actuation, couples the tangential inlet port with the powder composition in the received blister.

[0026] In certain variants of this embodiment, each blister contains a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof. In other variants, each blister contains a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material has an average particle size of from about 40 to about 70 microns, and at least 90 percent of said apomorphine has a particle size of 5 microns or less.

[0027] Although certain of the compositions, methods or treatment, inhalers, blisters, methods for inhaling, and doses have been described above as including a carrier material having a preferred average particle size of from about 40 microns to about 70 microns, it should be appreciated that in accordance with other embodiments, the carrier material in these compositions, methods or treatment, inhalers, blisters, methods for inhaling, and doses can have other average particle size ranges, for example, from about 10 microns to about 1000 microns, from about 10 microns to about 70 microns, or from about 20 microns to about 120 microns.

[0028] With regard to the aerosolising device, in certain variants of this embodiment, the aerosolising device is in the form a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and a substantially axial exit port, wherein the ratio of the diameter of the vortex chamber to the diameter of the exit port is between 4 and 12.

[0029] In other variants, the aerosolising device is in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port, wherein the inlet port has an outer wall which defines the maximum extent of the inlet port in the radially outward direction of the vortex chamber. The extent of the outer wall in the axial direction of the vortex chamber is substantially equal to the maximum extent of

the inlet port in the axial direction of the vortex chamber, and the outer wall is substantially parallel with a wall of the vortex chamber.

[0030] In other variants, the aerosolising device is in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port. An exit port is spaced from the inlet port in an axial direction. A bottom surface defines the furthest extent of the vortex chamber from the exit port in the axial direction, and the bottom surface further defines the furthest axial extent of the inlet port from the exit port.

[0031] In other variants, the aerosolising device is in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and an inlet conduit arranged to supply a powdered composition entrained in a gas flow to the inlet port, in use, wherein the cross-sectional area of the inlet conduit decreases towards the vortex chamber. The inlet conduit is, upon actuation of the inhaler, coupled to the powder composition in the received blister.

[0032] In other variants, the aerosolising device is in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and an arcuate inlet conduit arranged to supply a powdered composition entrained in a gas flow to the inlet port, in use. The inlet conduit is, upon actuation of the inhaler, coupled to the powder composition in the received blister.

[0033] In other variants, the aerosolising device is in the form of a vortex chamber having an axis and being defined, at least in part, by a wall which forms a curve about the axis. The vortex chamber has a cross-sectional area in a plane bounded by the axis, and the plane extends in one direction radially from the axis at a given angular position (θ) about the axis. The vortex chamber has a substantially tangential inlet port and a substantially axial exit port, and said cross-sectional area of the vortex chamber

decreases with increasing angular position (θ) in the direction, in use, of gas flow between the inlet port and the exit port.

[0034] In other variants, the aerosolising device is in the form of a vortex chamber having an axis and being defined, at least in part, by a wall which forms a curve about the axis. The vortex chamber has a substantially tangential inlet port and a substantially axial exit port. The vortex chamber is further defined by a base, and the distance (d) between the base and a plane which is normal to the axis and is located on the opposite side of the base to the exit port increases with radial position (r) relative to the axis.

[0035] In other variants, the aerosolising device includes a chamber defined by a top wall, a bottom wall, and a lateral wall, the lateral wall being curved about an axis which intersects the top wall and the bottom wall. The chamber encloses a cross-sectional area defined by the axis, the top wall, the bottom wall and the lateral wall, and the chamber has an inlet port and an outlet port. The inlet port is tangent to the lateral wall, the outlet port is co-axial with the axis, and the cross-sectional area decreases with increasing angular position from the inlet port in a direction of a gas flow through the inlet port.

[0036] In still other variants, the aerosolising device a chamber including a wall, a base, an inlet port and an exit port. The chamber has an axis that is co-axial with the exit port and intersects the base. The wall is curved about the base, the inlet port is tangential to the wall, and a height between the base and a plane normal to the axis at the exit port decreases as a radial position from the axis to the inlet port increases.

Brief Description of the Drawings

[0037] Figure 1 shows an inhaler and blister in accordance with an embodiment of the present invention.

[0038] Figure 2 is a top cross-section of a vortex nozzle 1.

[0039] Figure 3 is a side cross-section of a vortex chamber in accordance with an embodiment of the invention.

[0040] Figure 4 is a sectional view along line B-B of the vortex chamber of Figure 3.

[0041] Figure 5(a) is a side view of a vortex chamber with a round inlet port.

[0042] Figure 5(b) is a sectional view along line D-D of the vortex chamber of Figure 5(a).

[0043] Figure 6(a) is a side view of a vortex chamber with a rectangular inlet port.

[0044] Figure 6(b) is a sectional view along line E-E of the vortex chamber of Figure 6(a).

[0045] Figure 7 shows a vortex chamber with an arcuate inlet conduit.

[0046] Figures 8 to 11 show detail of embodiments of the exit port of the inhaler in accordance with the invention.

[0047] Figure 12 illustrates an asymmetric vortex chamber in accordance with an embodiment of the invention.

[0048] Figure 13 is a sectional view of a vortex chamber in accordance with another asymmetric inhaler in accordance with an embodiment of the invention.

[0049] Figure 14 is a perspective view of a vortex chamber according to Figure 13.

[0050] Figure 15 is a sectional view of the vortex chamber of Figure 14.

[0051] Figure 16 is a perspective view of a detail of the vortex chamber of Figures 14 and 15;

[0052] Figure 17 is a plan view of the detail of Figure 16.

[0053] Figure 18 is a plan view of a variation of the detail of Figure 17.

[0054] Figures 19 to 21 show variations of the interface between the wall and the base of a vortex chamber according to the embodiments of Figures 13-18.

[0055] Figures 22(A-B) illustrates the particle size distribution of the lactose of Example 1.

[0056] Figures 23(A-B) illustrate the particle size distribution of the micronized apomorphine of Example 2.

[0057] Figure 24 shows stability data for the 200 microgram apomorphine-lactose formulation of Examples 2(a) and 3.

[0058] Figure 25 shows a perspective view of the prototype inhaler used to perform inhalation testing in accordance with Example 4.

[0059] Figure 26 shows the inhaler of Figure 25 with its cover removed to show the breath actuation mechanism and vortex nozzle.

[0060] Figure 27 is a cross-section is a cross-section view through the vortex nozzle taken along line AA in Figure 26.

[0061] Figures 28A is a cross-section view taken along line BB in Figure 26 showing the nozzle valve in the closed position.

[0062] Figures 28B is a cross-section view taken along line BB in Figure 26 showing the nozzle valve in the open position.

[0063] Figures 29(A) and 29(B) illustrate the results of tests performed on the apomorphine-lactose formulation of Examples 2 and 3.

[0064] Figure 30 illustrate the particle size distribution of the micronized apomorphine of Example 10.

Detailed Description of the Preferred Embodiments

[0065] In a dry powder inhaler, the dose to be administered is stored in the form of a non-pressurized dry powder and, on actuation of the inhaler, the particles of the powder are inhaled by the patient. Dry powder inhalers can be "passive" devices in which the patient's breath is the only source of gas which provides a motive force in the device, or "active" devices in which a source of compressed gas is used. Examples of "passive" dry powder inhaler devices include the Rotahaler and Diskhaler (Glaxo-Wellcome) and the Turbohaler (Astra-Draco). Particularly preferred "active" dry powder inhalers will be described in more detail below in connection with Figures 1-21, 25-28(b). It should be appreciated, however, that the compositions of the present invention can be administered with either passive or active inhaler devices.

[0066] "Actuation of the inhaler" refers to the process during which a dose of the powder is removed from its rest position in the inhaler (e.g., a blister, reservoir, or other container) usually by a patient inhaling. That step takes place after the powder (or container or blister containing the powder) has been loaded into the inhaler ready for use.

[0067] While it is clearly desirable for as large a proportion as possible of the particles of active material to be delivered to the deep lung, it is usually preferable for as little as possible of the other components to penetrate the deep lung. Therefore, powders generally include particles of an active material, and carrier particles for carrying the particles of active material.

[0068] As described in WO 01/82906, published November 8, 2001, an additive material may also be provided in a dose which indicates to the patient that the dose has been administered. The additive material, referred to below as indicator material, may be present in the powder as formulated for the dry powder inhaler, or be present in a separate form, such as in a separate location within the inhaler such that the additive becomes entrained in the airflow generated on inhalation simultaneously or sequentially with the powder containing the active material.

[0069] In accordance with an embodiment of the present invention, an inhalable powder composition is provided which includes apomorphine or a pharmaceutically acceptable salt thereof (thereinafter collectively "apomorphine"), in combination with a carrier material. The apomorphine is provided in an amount from 100 micrograms to 1600 micrograms per unit dose, and is preferably provided in an amount from 100 micrograms to 800 micrograms per dose. Most preferably, the apomorphine is provided in an amount from 100 micrograms to 600 micrograms per dose.

[0070] In certain embodiments of the present invention, each dose is stored in a "blister" of a blister pack. In this regard, apomorphine is susceptible to oxidation, and, as such, it is important to prevent (or substantially limit) oxidation of the apomorphine prior to administration. In accordance with the embodiments of the present invention which utilize blisters, exposure of the formulation to air prior to administration (and unacceptable oxidation of the apomorphine) is prevented by storing each dose in a sealed blister. Most preferably, oxidation is further prevented (or limited) by placing a

plurality of blisters into a further sealed container, such as a sealed bag made, for example of a foil such as aluminum foil. The use of the sealed blisters (and optional sealed bags) eliminates any need to include anti-oxidants in the formulation.

[0071] For the effective administration by a dry powder inhaler of the particles of apomorphine material to the lung where they can be absorbed, the particle size characteristics of the powder are particularly important.

[0072] In particular, for the effective delivery of active material deep into the lung, the active particles should be small and well dispersed on actuation of the inhaler.

[0073] It is preferred for the powder to be such that a fine particle fraction of at least 35% is generated on actuation of the inhaler device. It is particularly preferred that the fine particle fraction be greater than or equal to 60%.

[0074] Thus, in certain embodiments of the present invention also provide a powder for use in an inhaler device, the powder comprising apomorphine or a pharmaceutically acceptable salt thereof in combination with a carrier material, the powder being such that it generates a fine particle fraction of at least 35%, preferably at least 45%, more preferably at least 50 % and most preferably at least 60%, on actuation of the inhaler device.

[0075] The term "fine particle fraction" is used herein to mean that fraction of the total amount of active material (in this case apomorphine or its pharmaceutically acceptable salts) delivered by a device which has a diameter of not more than 5μm. The total amount of active material delivered by a device is in general less than the amount of the active material that is metered in the device or is present in a pre-metered dose within the device.

[0076] Fine particle fractions referred to herein in relation to powders are as measured using a sample of the powder fired from a dry powder inhaler into a Multi Stage Liquid Impinger (MSLI) (United States Pharmacopeia (U.S.P) 26, chapter 601, Apparatus 4, (2003) Apparatus C, European Pharmacopoeia, Method 5.2.9.18, Supplement 2000) or Anderson Cascade Impactor (ACI)(U.S.P. 26, chapter 601, Apparatus 3 (2003)) . The powder is preferably such that a fine particle fraction of at least 35%, preferably at least 45%, more preferably at least about 50%, and most preferably at least about 60%, is generated on actuation of the inhaler device.

[0077] Most preferably, the inhaler device is a high turbulence inhaler device, the arrangement being such that a fine particle fraction of at least 35%, preferably at least 50%, and most preferably at least 60%, is generated on actuation of the inhaler device.

[0078] A "high turbulence inhaler device" is to be understood as meaning an inhaler device which is configured to generate relatively high turbulence within the device and/or a relatively high incidence of impaction of powder upon internal surfaces and/or obstructions within the device, whereby efficient de-agglomeration of agglomerated powder particles occurs in use of the device.

[0079] As noted above, in addition to the active material (and an indicator material if present), the powder preferably includes carrier material in the form of particles for carrying the particles of active material. The carrier particles may be composed of any pharmacologically inert material or combination of materials which is acceptable for inhalation.

[0080] Advantageously, the carrier particles are composed of one or more crystalline sugars; the carrier particles may be composed of one or more sugar alcohols or polyols. Preferably, the carrier particles are particles of dextrose or lactose, especially lactose.

[0081] Preferably, at least 90% by weight of the active material has a particle size of not more than 10 μm, most preferably not more than 5 μm. The particles therefore give a good suspension on actuation of the inhaler.

[0082] In embodiments of the present invention which utilize conventional inhalers , such as the Rotohaler, Diskhaler, and Turbohaler described above, the particle size of the carrier particles may range from about 10 microns to about 1000 microns. In certain of these embodiments, the particle size of the carrier particles may range from about 20 microns to about 120 microns. In certain other ones of these embodiments, the size of at least 90% by weight of the carrier particles is less than 1000 μm and preferably lies between 60μm and 1000 μm. The relatively large size of these carrier particles gives good flow and entrainment characteristics.

[0083] In these embodiments, the powder may also contain fine particles of an excipient material, which may for example be a material such as one of those mentioned above as being suitable for use as a carrier material, especially a crystalline sugar such as dextrose or lactose. The fine excipient material may be of the same or a different material from the carrier particles, where both are present. The particle size of the fine excipient material will generally not exceed 30μm, and preferably does not exceed 20 μm. In some circumstances, for example, where any carrier particles and/or any fine excipient material present is of a material itself capable of inducing a sensation in the oropharyngeal region, the carrier particles and/or the fine excipient material can constitute the indicator material. For example, the carrier particles and/or any fine particle excipient may comprise mannitol.

[0084] The powders may also be formulated with additional excipients to aid delivery and release. For example, powder may be formulated with relatively large carrier particles which aid the flow from the dry powder inhaler into the lung. Large carrier particles are known, and include lactose particles having a mass medium aerodynamic

diameter of greater than 90 microns. Alternatively, the hydrophobic microparticles may be dispersed within a carrier material. For example, the hydrophobic microparticles may be dispersed within a polysaccharide matrix, with the overall composition formulated as microparticles for direct delivery to the lung. The polysaccharide acts as a further barrier to the immediate release of the active agent. This may further aid the controlled release process. Suitable carrier materials will be apparent to the skilled person and include any pharmaceutically acceptable insoluble or soluble material, including polysaccharicles. An example of a suitable polysaccharide is xantham gum.

[0085] In some circumstances, the powder for inhalation may be prepared by mixing the components of the powder together. For example, the powder may be prepared by mixing together particles of active material and lactose.

[0086] The dry powder inhaler devices in which the powder compositions of the present invention will commonly be used include "single dose" devices, for example the Rotahaler, the Spinhaler and the Diskhaler in which individual doses of the powder composition are introduced into the device in, for example, a capsule, or a blister and also multiple dose devices, for example the Turbohaler in which, on actuation of the inhaler, one dose of the powder is removed from a reservoir of the powder material contained in the device.

[0087] As already mentioned, in the case of certain powders, a form of device that promotes high turbulence offers advantages in that a higher fine particle fraction will be obtainable than in the use of other forms of device. Such devices include, for example, the Turbohaler™ or Novolizer™, and may be devices of the kind in which generation of an aerosolized cloud of powder is driven by inhalation of the patient or of the kind having a dispersal device for generating or assisting in generation of the aerosolized cloud of powder for inhalation.

[0088] Where present, the amount of carrier particles will generally be up to 95%, for example, up to 90%, advantageously up to 80% and preferably up to 50% by weight based on the total weight of the powder. The amount of any fine excipient material, if present, may be up to 50% and advantageously up to 30%, especially up to 20%, by weight, based on the total weight of the powder.

[0089] In contrast to the particle sizes described above, in embodiments of the present invention which utilize an inhaler of the type described below in connection with Figures 1-21, 25-28, the carrier particles are preferably between 10 and 70 microns, and more preferably between 40 and 70 microns in diameter. Such a particle size can be achieved for example, by sieving the excipient through screens of 46 microns and 63 microns, thereby excluding particles that pass through the 46 micron screen, and excluding particles that do not pass through the 63 micron screen. Most preferably, the excipient is lactose. Preferably, at least 90 % (percent), and most preferably at least 99%, of the apomorphine particles are 5 microns or less in diameter.

[0090] The formulations described herein may also include one or more force control additives (FCAs), in an amount from about 0.1 % to about 10 % by weight, and preferably from about 0.15% to 5%, most preferably from about 0.5 % to about 2%. FCAs may include, for example, magnesium stearate, leucine, lecithin, and sodium stearyl fumarate, and are described more fully in U.S. Patent No. 6,153,224, which is hereby incorporated by reference.

[0091] When the FCA is micronized leucine or lecithin, it is preferably provided in an amount from about 0.1% to about 10% by weight, preferably about 0.5 % to about 5%, preferably about 2%, of micronized leucine. Preferably, at least 95% by weight of the micronized leucine has a particle diameter of less than 150 microns, preferably less than 100 microns, and most preferably less than 50 microns. Preferably, the mass median diameter of the micronized leucine is less than 10 microns.

[0092] If magnesium stearate or sodium stearyl fumate is used as the FCA, it is preferably provided in an amount from about 0.05% to about 5 %, preferably from about 0.15% to about 2%, most preferably from about 0.25 to about 0.5%.

[0093] Where reference is made to particle size of particles of the powder, it is to be understood, unless indicated to the contrary, that the particle size is the volume weighted particle size. The particle size may be calculated by a laser diffraction method. Where the particle also includes an indicator material on the surface of the particle, advantageously the particle size of the coated particles is also within the preferred size ranges indicated for the uncoated particles.

[0094] Figure 1 shows schematically a preferred inhaler that can be used to deliver the powder formulations described above to a patient. Inhalers of this type are described in WO 02/089880 and WO 02/089881, both published on November 14, 2002, the entire disclosures of which are hereby incorporated by reference. Figures 2-7 correspond to the inhalers described in WO 02/089880, Figures 12-21 correspond to the inhalers described in WO 02/089881, and Figures 8-11 show preferred exit port configurations that can be used in connection with any of these inhalers.

[0095] Referring to Figures 1 and 2, the inhaler comprises a nozzle 3000 including a vortex chamber 1 and having an exit port 2 and an inlet port 3 for generating an aerosol of the powder formulation. The vortex chamber 1 is located in a mouthpiece 10 through which the user inhales to use the inhaler. Air passages (not shown) may be defined between the vortex chamber 1 and the mouthpiece 10 so that the user is able to inhale air in addition to the powdered medicament.

[0096] The powder formulation is stored in a blister 60 defined by a support 70 and a pierceable foil lid 75. As shown, the support 70 has a cavity formed therein for holding the powder formulation. The open end of the cavity is sealed by the lid 75. An air inlet

conduit 7 of the the vortex chamber 1 terminates in a piercing head (or rod) 50 which pierces the pierceable foil lid 75. A reservoir 80 is connected to the blister 60 via a passage 78. A regulated air supply 90 charges the reservoir 80 with a gas (e.g., air, in this example) to a predetermined pressure (e.g. 1.5 bar). Preferably, the blister contains from 1 to 5 mg of powder formulation, preferably 1, 2 or 3 mg of powder formulation.

[0097] In certain embodiments, the support 70 is also made of foil. Such blisters are commonly referred to in the art as double-foil blisters. In other embodiments of the present invention, the support 70 is made of a polymer. It is believed that the foil support 70 provides greater protection against moisture and oxidation than the polymer support 70.

[0098] When the user inhales, a valve 40 is opened by a breath-actuated mechanism 30, forcing air from the pressurized air reservoir through the blister 60 where the powdered formulation is entrained in the air flow. The air flow transports the powder formulation to the vortex chamber 1, where a rotating vortex of powder formulation and air is created between the inlet port 3 and the outlet port 2. Rather than passing through the vortex chamber in a continuous manner, the powdered formulation entrained in the airflow enters the vortex chamber in a very short time (typically less than 0.3 seconds and preferably less than 20 milliseconds) and, in the case of a pure drug formulation (i.e., no carrier), a portion of the powder formulation sticks to the walls of the vortex chamber. This powder is subsequently aerosolised by the high shear forces present in the boundary layer adjacent to the powder. The action of the vortex deagglomerates the particles of powder formulation, or in the case of a formulation comprising a drug and a carrier, strips the drug from the carrier, so that an aerosol of powdered formulation exits the vortex chamber 1 via the exit port 2. The aerosol is inhaled by the user through the mouthpiece 10.

[0099] The vortex chamber 1 can be considered to perform two functions: deagglomeration, the breaking up of clusters of particles into individual, respirable

particles; and filtration, preferentially allowing particles below a certain size to escape more easily from the exit port 2. Deagglomeration breaks up cohesive clusters of powdered formulation into respirable particles, and filtration increases the residence time of the clusters in the vortex chamber 1 to allow more time for them to be deagglomerated. Deagglomeration can be achieved by creating high shear forces due to velocity gradients in the airflow in the vortex chamber 1. The velocity gradients are highest in the boundary layer close to the walls of the vortex chamber.

[0100] As shown in more detail in Figure 2, the vortex chamber 1 of Figures 2 through 7 is in the form of a substantially cylindrical chamber. The vortex chamber 1 has a frustoconical portion in the region of the exit port 2. The inlet port 3 is substantially tangential to the perimeter of the vortex chamber 1 and the exit port 2 is generally concentric with the axis of the vortex chamber 1. Thus, gas enters the vortex chamber 1 tangentially via the inlet port 3 and exits axially via the exit port 2. Between the inlet port 3 and the exit port 2 a vortex is created in which shear forces are generated to deagglomerate the particles of medicament. The length of the exit port 2 is preferably minimized to reduce the possibility of deposition of the drug on the walls of the exit port 2. In the embodiment shown, the vortex chamber 1 is machined from polyetheretherketone (PEEK), acrylic, or brass, although a wide range of alternative materials is possible.

[0101] The ratio of the diameter of the vortex chamber to the diameter of the exit port can be significant in maximising the fine particle fraction of the medicament aerosol which is expelled from the exit port. Thus, the ratio of the diameter of the vortex chamber to the diameter of the exit port may be between 4 and 12. It has been found that when the ratio is between 4 and 12 the proportion of particles of the powdered medicament with an effective diameter in the range 1 to 3 microns is maximised. For an enhanced fine particle fraction, the ratio is preferably greater than 5, most preferably greater than 6 and preferably less than 9, most preferably less than 8. In the preferred arrangement, the ratio is 7.1.

[0102] In certain embodiments of the invention, the diameter of the vortex chamber is between 2 and 12 mm. The diameter of the vortex chamber is preferably greater than 4 mm, most preferably at least 5 mm and preferably less than 8 mm, most preferably less than 6 mm. In the preferred embodiment, the diameter of the vortex chamber is 5 mm. In these embodiments, the height of the vortex chamber is generally between 1 and 8 mm. The height of the vortex chamber is preferably less than 4 mm, most preferably less than 2 mm. In the preferred embodiment, the height of the vortex chamber is 1.6 mm. In general, the vortex chamber is substantially cylindrical. However, the vortex chamber may take other forms. For example, the vortex chamber may be frustoconical. Where the diameter of the vortex chamber or the exit port is not constant along its length, the ratio of the largest diameter of the vortex chamber to the smallest diameter of the exit port should be within the range specified above. The aerosolising device comprises an exit port, for example as described above. The diameter of the exit port is generally between 0.5 and 2.5 mm. The diameter of the exit port is preferably greater than 0.6 mm and preferably less than 1.2 mm, most preferably less than 1.0 mm. In the preferred embodiment, the diameter of the exit port is 0.7 mm.

Dimension		Preferred Value
D	Diameter of chamber	5,0 mm
H	Height of chamber	1.6 mm
h	Height of conical part of chamber	0.0 mm
D_e	Diameter of exit port	0.7 mm
t	Length of exit port	0.3 mm
a	Height of inlet port	1.1 mm
b	Width of inlet port	0.5 mm
α	Taper angle of inlet conduit	12°

Table 1 - Symmetrical Vortex chamber dimensions

[0103] Figures 3 and 4 show the general form of the vortex chamber of the inhaler of Figure 1. The geometry of the vortex chamber is defined by the dimensions listed in Table 1. The preferred values of these dimension are also listed in Table 1. It should be noted that the preferred value of the height h of the conical part of the chamber is 0 mm, because it has been found that the vortex chamber functions most effectively when the top of the chamber is flat.

[0104] As shown in Table 2, the proportion of the particles of medicament emitted in the aerosol having an effective particle diameter of less than 6.8 microns generated by the vortex chamber (the 6.8 micron particle fraction) depends on the ratio of the diameters of the chamber D and the exit port D_e. The normalised average 6.8 micron particle fraction is the emitted 6.8 micron particle fraction divided by the 6.8 micron particle fraction of the powdered medicament loaded into the inhaler. The medicament used was pure Intal™ sodium cromoglycate (Fisons UK).

Ratio D/D_e	Average particle fraction that is less than 6.8 μm	Normalised average particle fraction that is less than 6.8 μm
2.0	64.7%	73.1%
3.1	70.8%	79.9%
4.0	75.5%	85.2%
6.0	81.0%	91.4%
7.1	83.5%	94.3%
8.0	83.2%	93.9%
8.6	80.6%	91.0%

Table 2 - Relationship between emitted 6.8 micron particle fraction and ratio of vortex chamber diameter to exit port diameter.

[0105] It will be seen from the above table that where the ratio of the diameters of the chamber and the exit port is 4 or more, the normalised 6.8 micron particle fraction is over 85%. Thus, the deagglomeration efficiency of the vortex chamber is significantly improved where the ratio is in this range. With the preferred ratio of 7.1, a normalised 6.8 micron particle fraction of 94.3% has been achieved.

[0106] Figures 5a and 5b show a vortex chamber 1 in which the inlet port 3 has a circular cross-section. As represented by the solid arrow in Figure 5b, a portion of the airflow entering the vortex chamber via the inlet port 3 follows the lateral wall 12 of the vortex chamber 1. The powder entrained in this airflow is therefore introduced directly into the airflow at the boundary layer adjacent the lateral wall 12 of the vortex chamber 1, where the velocity gradient in the radial direction is at a maximum. The maximal velocity gradient results in maximal shear forces on the agglomerated particles of the powder and thus maximum deagglomeration.

[0107] However, as represented by the dashed arrow in Figure 5b, a portion of the airflow entering the vortex chamber via the inlet port 3 does not follow the chamber wall 12, but rather crosses the chamber 1 and meets the wall 12 at a point opposite the inlet port 3. At this point, there is increased turbulence, because the flow must make an abrupt change of direction. This turbulence disturbs the boundary layer adjacent the wall 12 of the chamber 1 and thereby reduces the effectiveness of the deagglomeration of the powder.

[0108] Figures 6a and 6b show a vortex chamber 1 in which the inlet port 3 has a rectangular cross-section. The rectangular cross-section maximises the length of the perimeter of the inlet port that is coincident with the wall 12 of the vortex chamber 1, such that the maximum air flow is introduced into the boundary layer of the vortex. Similarly, the rectangular cross-section maximises the width of the perimeter of the inlet port 3 that is coincident with the bottom surface 13 of the vortex chamber 1. In

this way, deposition of powder in the vortex chamber 1 is prevented, because the vortex occupies the entire chamber 1.

[0109] In addition to having a rectangular cross-section, the inlet port 3 of Figures 6a and 6b is supplied by an inlet conduit 7 which tapers towards the vortex chamber 1. Thus, the inlet conduit 7 is defined by an inner wall 14 and an outer wall 15. The outer wall 15 is substantially tangential to the wall 12 of the vortex chamber 1. The spacing of the inner wall 14 from the outer wall 15 decreases towards the vortex chamber 1, so that the inner wall 14 urges the air flow into the vortex chamber 1 towards the boundary layer.

[0110] Furthermore, the decreasing cross-sectional area of the inlet conduit 7 causes the flow of velocity to increase, thereby reducing deposition of powder on the way to the vortex chamber 1.

[0111] As indicated by the arrows in Figure 6b, all of the airflow entering the vortex chamber via the inlet port 3 follows the wall 12 of the vortex chamber 1. The powder entrained in this airflow is therefore introduced directly into the airflow at the boundary layer adjacent the wall 12 of the vortex chamber 1, and deagglomeration is maximised.

[0112] A further improvement can also be achieved if the upper surface 16 of the vortex chamber 1 is flat, as shown in Figures 8 to 10, rather than conical as shown in Figures 1, 3, 5 and 6. Thus, in this arrangement, the upper surface 16 of the vortex chamber 1 is substantially perpendicular to the wall 12 of the chamber 1, and to the axis of the vortex.

[0113] Figures 8 to 11 show various options for the exit port 2 of the vortex chamber 1. The characteristics of the exit plume of the aerosol are determined, at least in part, by the configuration of the exit port 2. For example, if the aerosol leaves an exit port 2

of 1 mm diameter at a flow rate of 2 litres/minute, the velocity at the exit port 2 will be approximately 40 m/s. This velocity can be reduced to a typical inhalation velocity of 2 m/s within a few centimetres of the chamber or nozzle by providing a strongly divergent aerosol plume.

[0114] In Figure 8, the exit port 2 is a simple orifice defined through the upper wall 17 of the vortex chamber 1. However, the thickness of the upper wall 17 means that the exit port 2 has a length which is greater than its diameter. Thus, there is a risk of deposition in the exit port as the aerosol of powder exits. Furthermore, the tubular exit port tends to reduce the divergence of the exit plume. These problems are solved in the arrangement of Figure 9 by tapering the upper wall 17 of the vortex chamber 1 towards the exit port 2 so that the exit port 2 is defined by a knife edge of negligible thickness. For an exit port 2 of diameter 1 mm, an exit port length of 2.3 mm gives a plume angle of 60°, whereas reducing this length to 0.3 mm increases the angle to 90°.

[0115] In Figure 10, the exit port 11 is annular and is also defined by a knife edge. This arrangement produces an exit plume that slows down more quickly than a circular jet, because the annular exit port has a greater perimeter than a circular port of the same diameter and produces a jet that mixes more effectively with the surrounding static air. In Figure 11, multiple orifices form the exit port 2 and produce a number of smaller plumes which break up and slow down in a shorter distance than a single large plume.

[0116] Figure 7 shows an embodiment of the vortex chamber 1 in which the inlet conduit 7 is arcuate and tapers towards the vortex chamber 1. As shown by the arrows in Figure 13, the arcuate inlet conduit 7 urges the entrained particles of powdered formulation towards the outer wall 15 of the inlet conduit 7. In this way, when the powder enters the vortex chamber 1 through the inlet port 3 the powder is introduced directly into the boundary layer next to the wall 12 of the vortex chamber 1, where shear forces are at a maximum. In this way, improved deagglomeration is achieved.

[0117] The inhaler in accordance with embodiments of the invention is able to generate a relatively slow moving aerosol with a high fine particle fraction. The inhaler is capable of providing complete and repeatable aerosolisation of a measured dose of powdered drug and of delivering the aerosolised dose into the patient's inspiratory flow at a velocity less than or equal to the velocity of the inspiratory flow, thereby reducing deposition by impaction in the patient's mouth. Furthermore, the efficient aerosolising system allows for a simple, small and low cost device, because the energy used to create the aerosol is small. The fluid energy required to create the aerosol can be defined as the integral over time of the pressure multiplied by the flow rate. This is typically less than 5 joules and can be as low as 3 joules.

[0118] Figures 12-21 show asymmetric inhalers in accordance with other embodiments of the present invention with similar components bearing identical reference numbers to the embodiments described above.

[0119] Initially, it should be noted that the difference between these embodiments and the embodiments described above with regard to Figures 1-11 is that, in the embodiments shown in Figures 12-21, the vortex chamber 1 has an asymmetric shape.

[0120] In the embodiment shown in Figure 12, the wall 12 of the vortex chamber 1 is in the form of a spiral or scroll. The inlet port 3 is substantially tangential to the perimeter of the vortex chamber 1 and the exit port 2 is generally concentric with the axis of the vortex chamber 1. Thus, gas enters the vortex chamber 1 tangentially via the inlet port 3 and exits axially via the exit port 2. The radius R of the vortex chamber 1 measured from the centre of the exit port 2 decreases smoothly from a maximum radius R_{max} at the inlet port 3 to a minimum radius R_{min}. Thus, the radius R at an angle θ from the position of the inlet port 3 is given by $R=R_{max}(1-\theta k/2\pi)$, where $k=(R_{max}-R_{min})/R_{max}$. The effective radius of the vortex chamber 1 decreases as the air flow and entrained particles of medicament circulate around the chamber 1. In this way, the effective

cross-sectional area of the vortex chamber 1 experienced by the air flow decreases, so that the air flow is accelerated and there is reduced deposition of the entrained particles of medicament. In addition, when the flow of air has gone through 2π radians (360°), the air flow is parallel to the incoming airflow through the inlet port 3, so that there is a reduction in the turbulence caused by the colliding flows.

[0121] Between the inlet port 3 and the exit port 2 a vortex is created in which shear forces are generated to deagglomerate the particles of the powdered formulation. As discussed above, the length of the exit port 2 is preferably as short as possible to reduce the possibility of deposition of the drug on the walls of the exit port 2. In the embodiment shown, the vortex chamber 1 is machined from PEEK, acrylic, or brass, although a wide range of alternative materials is possible. For manufacturing ease, the radius of the vortex chamber 1 may decrease in steps rather than smoothly.

[0122] Figure 13 shows the general form of the vortex chamber of the inhaler of Figure 12. The geometry of the vortex chamber is defined by the dimensions listed in Table 3. The preferred values of these dimension are also listed in Table 3. It should be noted that the preferred value of the height h of the conical part of the chamber is 0 mm, because it has been found that the vortex chamber functions most effectively when the top (roof 16) of the chamber is flat.

Dimension		**Preferred Value**
R_{max}	Maximum radius of chamber	2.8 mm
R_{min}	Minimum radius of chamber	2.0 mm
H_{max}	Maximum height of chamber	1.6 mm
h	Height of conical part of chamber	0.0 mm
D_e	Diameter of exit port	0.7 mm
t	Length of exit port	0.3 mm
a	Height of inlet port	1.1 mm

Dimension		Preferred Value
b	Width of inlet port	0.5 mm
α	Taper angle of inlet conduit	9°, then 2°

Table 3- Asymmetrical Vortex chamber dimensions

[0123] The 6.8 micron particle fraction of the aerosol generated by the vortex chamber 1 according to Figure 12 is improved relative to a circular vortex chamber of Figures 1-11.

[0124] Figures 14 to 18 show another asymmetric inhaler in accordance with the present invention in which the vortex chamber 1 includes a ramp 20 which reduces the height of the vortex chamber 1 from the bottom up with increasing angular displacement θ from the inlet port 3. A substantially circular region 21 in the centre of the vortex chamber 1 remains flat.

[0125] Various options for the cross-section of the ramp 20 are shown in Figures 19 to 21. As shown in Figure 19, the cross-section of the ramp 20 may be a curve, such as a conic section. The value of the radius (or radii) of the curve may increase with increasing angular displacement θ about the axis of the vortex chamber 1.

[0126] Preferably, as shown in Figure 20, the ramp 20 has a triangular cross-section, with an angle β between the base and the upper surface of the ramp 20. The angle β is a function of the angular displacement θ, such that $\beta=q(\theta-\theta_1)$ where θ_1 and q are constants.

[0127] As shown in Figure 21, the joints between the ramp 20 and the wall 12 of the vortex chamber and the ramp 20 and the base of the vortex chamber 1 are curved, for example with a fillet radius, to prevent unwanted deposition in this region.

[0128] The vertical face (normal to the base) of the ramp 20 where the ramp meets the inlet 3 is likely to attract deposition because of the abrupt change in height. However, by arranging the profile of the face (looking axially) to form a smooth entry, as shown in Figure 17, contiguous with the inner edge of the inlet 3 air travelling from the inlet scours the face and prevents powder build up.

[0129] In one arrangement the profile is a straight line at 40° (angle ϕ in Figure 18) to the centre line of the inlet, joined to the inlet wall by a tangent curve. This profile follows the pattern of deposition that would be seen in a similar nozzle without a ramp.

[0130] In a preferred embodiment the profile is a curve moving radially inward as shown in Figure 17. At one end it joins the inner wall of the inlet tangentially. At the other end it joins a continuation of the inner curve of the ramp at the point where the ramp meets the base.

EXAMPLES

Example 1: Preparation of Lactose

[0131] A sieved fraction of Respitose SV003 (DMV International Pharma, The Netherlands) lactose is manufactured by passing bulk material through a 63 μm sieve. This material is then sieved through a 45 μm screen and the retained material is collected. Figures 22(A) and 22(B) show the results of a particle size analysis of two batches of the lactose performed with a Mastersizer 2000, manufactured by Malvern Instruments, Ltd. (Malvern, UK). As shown, the lactose had a volume weighted mean of from about 50 to about 55 microns, a d_{10} of from about 4 to about 10 microns, a d_{50} of from about 50 to about 55 microns, and a d_{90} of from about 85 to about 95 microns wherein d_{10} d_{50} d_{90} refer to the diameter of 10%, 50%, and 90% of the analyzed lactose.

Example 2: Preparation of Apomorphine-Lactose Formulation

[0132] Apomorphine hydrochloride was obtained from Macfrarian Smith Ltd, and was micronized according to the following product specification: >= 99.9% by mass < 10 microns, based upon a laser diffraction analysis. Actual typical results of the laser fraction analysis were as follows: d_{10} < 1 micron, d_{50}: 1-3 microns; d_{90}<6 microns, wherein d_{10} d_{50} d_{90} refer to the diameter of 10%, 50%, and 90% of the analyzed apomorphine hydrochloride. The apomorphine hydrochloride was micronized with nitrogen, (rather than the commonly employed air) to prevent oxidative degradation. Figures 23(A) and 23(B) show the results of a particle size analysis of two batches of the micronized apomorphine hydrochloride performed with the Mastersizer 2000, manufactured by Malvern Instruments, Ltd. (Malvern, UK).

Example 2(a) Preparation of 200 microgram Formulation

[0133] 70 grams of the lactose of Example 1 was placed into a metal mixing vessel of a suitable mixer. 10 grams of the micronized apomorphine hydrochloride were then added. An additional 70 grams of the lactose of Example 1 was then added to the mixing vessel, and the resultant mixture was tumbled for 15 minutes. The resultant blend was then passed through a 150 μm screen. The screened blend (i.e. the portion of the blend that passed through the screen) was then reblended for 15 minutes.

[0134] The particle size distribution of the apomorphine-lactose powder, as determined by an Andersen Cascade Impactor (U.S.P. 26, chapter 601, Apparatus 3 (2003)), showed that the drug particles were well dispersed. In particular, the particle size distribution for a 200 μg dose was as follows:

Fine particle dose (< 5 μm)	117 μg
Ultrafine particle dose (< 2.5 μm)	80 μg
MMAD (Mass Median Aerodynamic Diameter)	1.94 μm

Example 2(b) Preparation of 100 microgram Formulation

[0135] 72.5 grams of the lactose of Example 1 was placed into a metal mixing vessel of a suitable mixer. 5 grams of the micronized apomorphine hydrochloride were then added. An additional 72.5 grams of the lactose of Example 1 was then added to the mixing vessel, and the resultant mixture was tumbled for 15 minutes. The resultant blend was then passed through a 150 μm screen. The screened blend (i.e. the portion of the blend that passed through the screen) was then reblended for 15 minutes.

[0136] As described below with reference to Figures 29(A) and 29(B), in certain batches of Examples 2(a) and 2(b), the mixer used was an Inversina Variable Speed Tumbler Mixer, which is a low shear mixer distributed by Christison Scientific Equipment Ltd of Gateshead, U.K.. In other batches, the mixer used was a Retch Grindomix mixer is a higher shear mixer which is also distributed by Christison Scientific Equipment Ltd. Disaggregation was shown to be sensitive to the intensity of the mixing process but a consistent fine particle fraction (about 60%) was obtained using a low shear mixer equipped with a metal vessel such as the Inversina mixer referenced above.

Example 3: Incorporation of Formulation into Blisters

[0137] The formulations of Example 2(a) and 2(b) were each incorporated into blisters in the following manner. Three milligrams of the apomorphine-lactose formulation were placed in each blister. As described above in connection with Figure 1, the base of each blister is a cold-formed aluminum blister, formed from a laminate of oriented polyamide (exterior), 45 microns of aluminum (center), and PVC (interior). The lid of the blister is made of a hard-rolled 30 micron lidding foil, having a heat seal laquer. After the formulation is loaded into the interior of the blisters, the blisters are sealed by placing the lid over the blister base, and heat sealing the lid to the base via the heat seal laquer.

Example 4: Stability Data

[0138] The above-referenced blisters containing the apomorphine-lactose formulations of Example 2(a) were placed into aluminum bags to replicate patient packs, and stored for one month at 25 C and 60% relative humidity, and for one month at 40 C and 75% relative humidity (accelerated storage conditions). The formulation was then removed from the blisters and tested using High Performance Liquid Chromatography (HPLC). The results are shown in Figure 24. The assay value is the percent of the expected apomorphine content of the formulation, the "Rel Subs (highest individual peak %)" is the largest related substance peak as a percentage of the total peaks in the chromatogram; and the "Rel Subs (sum of related substance peaks)" is the total related substance peaks as a percentage of the total peak area in the chromatogram. As one of ordinary skill in the art will appreciate, these values are well within the pertinent ICH guidelines parameters of 0.2% for Rel Subs (highest individual peak %) and 1.0% for Rel Subs (sum of related substance peaks).

Example 5: Inhalation Testing

[0139] The above referenced blisters containing the 100 and 200 microgram apomorphine-lactose formulations were subjected to testing using the prototype inhaler shown in Figures 25 through 28. Referring to Figure 25 and 26, the inhaler comprises a reservoir 80 (not shown) which provides a charge of compressed air, a base block 2000, an airway 2004, a mouthpiece 10 through which the dose is inhaled, a blister loader 2010 by which the dose is presented to the inhaler, a crank arm 2015 by which the dose blister (60-70) is pierced, a vortex nozzle 3000 for aerosolizing the dose, and an exit valve 2020 by which the aerosolized dose is released into the mouthpiece 10.

[0140] In use, the user places a foil blister (not shown) onto the blister loader 2010 and inserts the blister loader into the device in the position shown in Fig.25. The user then pierces the blister by moving the crank arm 2015 from a rest position to a pierce position in which it locks. The reservoir 80 is then charged from a compressed air line (not shown) such that the reservoir 80 contains a volume of pressurized air (typically

15ml) at a relatively low pressure (typically 1.5bar gauge). The compressed air is prevented from leaving the device by the valve 2020 at the exit to the vortex nozzle 3000. The device is now primed to deliver the dose.

[0141] When the user inhales via the mouthpiece, breath actuation vane 2025 moves, opening the exit valve 2020 and releasing the compressed air in the reservoir. The air flows through the blister, entraining the dose of powder and carrying it to the vortex nozzle 3000. In the nozzle the powder experiences high centrifugal and shear forces which deagglomerate the dose before delivering it to the user via the mouthpiece 10 as a finely dispersed aerosol.

[0142] Referring to Figure 27, the vortex nozzle 3000 comprises an inlet conduit 3, a vortex chamber 1, an outlet port 2 and a nozzle seal 3010. In use, the compressed gas and entrained dry powder dose from the blister (not shown) enters the vortex chamber via an inlet tube 7 and inlet conduit 3 and leaves the nozzle 3000 via the exit port 2. At the point 3020 where the inlet conduit 3 joins the vortex chamber 1, the outer wall of the chamber has a radius of 3.35mm. Continuing counter-clockwise along the wall of the chamber 1 for 180 degrees, the radius of the chamber reduces linearly to 2.5mm at point 3025. The radius is then constant at 2.5mm as the wall of the chamber continues in counter-clockwise direction until it intersects the inlet conduit. The height of the vortex chamber is 1.6mm. The inlet tube 7 has an internal diameter of 1.22mm and feeds into the inlet conduit 3.

[0143] The inlet conduit 3 tapers in section from a 1.22mm diameter where it joins the inlet tube 7 to its narrowest point where the inlet conduit 3 joins the vortex chamber 1 and has a height of 1.1mm high and a width of 0.5mm. As such, the inlet conduit 3 does not extend to the full height of the vortex chamber, which is 1.6 mm. The outlet port 2 diameter is 0.7mm and the thickness of the outlet port 2 is 0.35mm.

[0144] Referring to Figures 26, 28A and 28B, the breath actuated mechanism comprises a valve 2020 at the outlet port of the vortex nozzle, a valve spring 2030 biased to open the valve, a breath actuation vane 2040 that rotates in response to inhalation by a user, and an inspiratory air inlet 2035 through which air is drawn when a user inhales through the mouthpiece 10. The valve 2020 includes a resilient valve seal 2023 mounted on a valve arm 2022 which in turn is rotatably mounted on a valve arm pivot 2021. When the valve arm 2022 is in the closed position (Figure 28A), the valve seal 2023 covers and seals the vortex nozzle outlet port 2. In the open position (Figure 28B) the vortex nozzle outlet port 2 is open to allow the dose to exit the nozzle 3000.

[0145] The breath actuation vane 2040 is rotatably mounted on a vane pivot 2045. The vane 2040 includes a vane roller 2046 which is rotatably mounted on the vane 2045 and is free to rotate, and a vane return spring (not shown) which biases the vane 2040 to the closed position as shown in Fig 28A. When the valve 2040 is in the closed position, the valve seal 2023 is compressed to seal the nozzle outlet 2 and the opposite end of the valve arm 2022 rests on the vane roller 2046 and is prevented from rotating.

[0146] When a user inhales through the mouthpiece10, air flows into the airway via the inspiratory air inlet 2035. This flow and the pressure drop it generates across the breath actuation vane 2040 cause the vane 2040 to rotate about its pivot 2045. The vane roller 2046 rolls against the end of the valve arm 2022 and then becomes clear of the valve arm 2022 as the vane 2040 rotates further. This allows the valve arm 2022 to rotate under the influence of the valve spring 2030, which removes the valve seal 2023 from the output port 2 (i.e., opening the valve) to release the dose from the nozzle as shown in Figure 28B.

[0147] The breath actuated mechanism can be reset for the next dose by rotating the valve reset lever 2050 through 90 degrees and then returning it to its original position. The reset lever 2050 acts on the valve arm 2022 to close the valve (by causing the valve

seal 2023 to cover output port 2) and allow the breath actuation vane 2040 to return to its closed position under the influence of the vane return spring (not shown).

[0148] In order to obtain the inhalation data described below, the inhaler of Figures 25 through 28 was used in conjunction with three instruments, a Multi-Stage Liquid Impinger (MSLI) (U.S.P. 26, chapter 601, Apparatus 4 (2003), an Anderson Cascade Impactor (ACI) (U.S.P. 26, chapter 601, Apparatus 3 (2003), and a Dosage Unit Sampling Apparatus (DUSA) (U.S.P. 26 chapter 601, Apparatus B (2003). Each of these devices have an input for receiving the mouthpiece 10 of the inhaler of Figures 25-28 .

[0149] The DUSA is used to measure the total amount of drug which leaves the inhaler. With data from this device, the metered and delivered dose is obtained. The delivered dose is defined as the amount of drug that leaves the inhaler. This includes the amount of drug in the throat of the DUSA device, in the measuring section of the DUSA device and the subsequent filters of the DUSA device. It does not include drug left in the blister or other areas of the inhaler of Figures 25-28, and does not account for drug "lost" in the measuring process of the DUSA device. The metered does includes all of the drug which leaves the blister.

[0150] The MSLI is a device for estimating deep lung delivery of a dry powder formulation. The MSLI includes a five stage cascade impactor which can be used for determining the particle size (aerodynamic size distribution) of Dry Powder Inhalers (DPIs) in accordance with USP 26, Chapter 601 Apparatus 4 (2003) and in accordance with the European Pharmacopoeia., Method 5.2.9.18, Apparatus C, Supplement 2000.

[0151] The ACI is another device for estimating deep lung delivery of a dry powder formulation. The ACI is multi-stage cascade impactor which can be used for

determining the particle size (aerodynamic size distribution) of Dry Powder Inhalers (DPI) in accordance with USP 26, Chapter 601 Apparatus 3 (2003).

[0152] As described below, the MSLI and the ACI testing devices can be used to determine, inter alia, the fine particle dose, or FPD (the amount of drug, e.g., in micrograms, that is measured in the sections of the testing device which correlates with deep lung delivery) and the fine particle fraction, or FPF, (the percentage of the metered dose which is measured in the sections of the testing device which correlates with deep lung delivery).

[0153] Figures 29(A) and 29(B) illustrate the results of tests performed on the apomorphine-lactose formulation of Example 2, using the inhaler of Figures 25-28. In Figure 29(a), data is shown for six formulations, which are identified in column 5000. Figure 29(b) provides data for an additional four formulations. In each Figure, the test data for the formulations is divided into two types: data related to uniformity of the delivered dose for the formulations (column 6000) and data related to fine particle size performance of the formulations (column 7000).

[0154] Referring to Figure 29(a), the first five formulations listed in column 5000 include 3 mg. of the 100 microgram formulation of Example 2(B). The sixth formulation listed includes 3 mg. of the 200 microgram formulation of Example 2(A). The first, second, and sixth formulation listings in 5000 contain the notation "Inversina" to indicate that the mixer used in Example 2 was the Inversina Mixer, and the third, fourth, and fifth formulation listing contain the notation "Grindomix" to indicate that the mixer used in Example 2 was the Grindomix Mixer. The second and fourth formulations listed also contain the notation "Air Jet" to indicate that for these formulations the lactose in Example 1 was sieved with an Air Jet Sieve which applies a vacuum to the screen Sieve apparatus, rather than a conventional screen Sieve (which was used for the first third, fifth, and sixth formulations listed). The fifth formulation

listed also contains the notation "20-30 μm Extra Fine" to indicate that the lactose for this formulation was screen sieved through 20 micron and 30 micron screens.

[0155] In section 6000 of Figure 29(a) the DUSA apparatus described above is used to provide data for the formulations regarding the drug retention in the blister (6012), the drug retention in the inhaler (6013), the delivered dose (6015), the metered dose (6020), and the mass balance percentage (6025). The notation n=10 indicates that the inhaler and DUSA apparatus was fired 10 times for each of the three formulations for which DUSA data is listed. The data listed in section 6000 is an average of the 10 firings.

[0156] In section 7000 of Figure 29(a), the fine particle performance is measured with two different devices, the MSLI and the ACI. Data for the ACI, where available, is indicated in parenthesis (). In any event, the data provided in section 7000 is for particles having a particle size diameter of less than 5 microns (referred to in this discussion as "fine particles"). As such, column 7012 provides the fine particle drug retention in the blister, column 7013 provides the fine particle drug retention in the inhaler, column 7015 provides the amount of fine particles in the delivered dose, column 7020 provides the FPD for the formulation, column 7025 provides the FPF for the formulation, column 7015 provides the amount of fine particles in the metered dose, column 7035 provides the mass balance percentage for the formulations in the MSLI (ACI) tests, and column 7036 provides the test flow rate for the formulations. Column 7005 indicates that the number of times the inhaler and MSLI (or ACI) apparatus were fired, and the data listed is an average of the "n" firings.

[0157] Figure 29(b) is similar to Figure 29(a), with similar items bearing identical reference numbers. The first formulation listed in column 5000 include 3 mg. of the100 microgram formulation of Example 2(b), the remaining four formulations include 3 mg. of the 200 microgram formulation of Example 2(a), and all of the formulations were made with the Inversina Mixer, and were sieved with 43 and 63 micron screens. The DUSA data in column 6000 was obtained in the same manner as

in Figure 29(a), except that n=11. All of the fine particle performance data in section 7000 was obtained using the ACI apparatus with n= 2, and a flow rate of 60 L min^{-1}.

[0158] As illustrated in Figure 29(a) and 29(b), when the formulations were mixed using the low shear Inversina mixer, the fine particle fraction (FPF) ranged from a low of 62% to a high of 70 %, and the percent delivered dose ranged from a low of 81 % to a high of 94%. The formulations made with the higher shear Grindomix mixer exhibited a fine particle fraction of from 47 % to 50 % for formulations including the 43-63 micron lactose. The formulation made with the high shear Grindomix mixer and with lactose sieved at 20 and 30 microns exhibited an increased fine particle fraction of 62 %.

Example 6: Preparation of 400 microgram formulation in 3 Mg Blister

[0159] A 400 microgram formulation can be manufactured in the manner set forth above with regard to Example 2, with the components provided in the following amounts:

Composition	Amount (µg)	Percent
Apomorphine Hydrochloride	400	13.33
Lactose	2600	86.66
Total	3000	100

Example 7: Preparation of 600 microgram formulation in 3 Mg Blister

[0160] A 600 microgram formulation can be manufactured in the manner set forth above with regard to Example 2, with the components provided in the following amounts:

Composition	Amount (µg)	Percent
Apomorphine Hydrochloride	600	20
Lactose	2400	80
Total	3000	100

[0161] Although the above referenced examples utilize a blister "fill weight" of 3 mg, it should be appreciated that larger or smaller fill weights may also be used. For example, in Examples 8-12 below, fill weights of 1 mg or 2 mg are provided. Although a variety of techniques for filling blisters to such fill weights may be used, it is believed that commercial production of blisters with 1 mg and 2 mg fill weights can be achieved with a Harro-Hoefliger Omnidose Drum Filter. Lower fill weights, and in particular fill weights on the order of 1 mg, are believed to provide superior fine particle fractions as compared to higher fill weights. For example, in experiments performed using an ACI with a single "shot", a 200 microgram apomorphine hydrochloride formulation as described above provided a fine particle fraction of 73% with a 3mg fill weight, 71% with a 2mg fill weight, and 83% with a 1 mg fill weight.

Example 8: Preparation of 800 microgram formulation in 2 Mg Blister

[0162] An 800 microgram formulation can be manufactured in the manner set forth above with regard to Example 2, with the components provided in the following amounts:

Composition	Amount (μg)	Percent
Apomorphine Hydrochloride	800	26.66
Lactose	1200	73.33
Total	2000	100

Example 9: Preparation of 200 microgram formulation with Magnesium Stearate in 1 Mg Blister

[0163] A 200 microgram formulation with Magnesium Stearate with the components provided in the following amounts:

Composition	Amount (μg)	Percent
Apomorphine Hydrochloride	200	20.00
Lactose	797.5	79.75
MgStearate	2.5	00.25
Total	1000	100

This formulation is prepared in the manner set forth above with regard to Example 2, except that Magnesium Stearate is added to the mixture along with the apomorphine hydrochloride.

Example 10: Preparation of 400 microgram formulation with Leucine in 2 Mg Blister

[0164] A 400 microgram formulation with Magnesium Stearate with the components provided in the following amounts:

Composition	Amount (μg)	Percent
Apomorphine Hydrochloride	400	20
Lactose	1560	78
Micronized Leucine	40	2
Total	2000	100

This formulation is prepared in the manner set forth above with regard to Example 2, except that micronized leucine is added to the mixture along with the apomorphine hydrochloride. Figure 30 shows the results of a particle size analysis of a preferred micronized Leucine performed with the Mastersizer 2000, manufactured by Malvern Instruments, Ltd. (Malvern, UK). As illustrated, the exemplified micronized leucine has a volume weighted mean particle diameter of 3.4 microns, with 90 % of the particles having a volume weighted mean particle diameter of less than 6 microns.

Example 11: Preparation of 200 microgram formulation in 2 Mg Blister

[0165] A 200 microgram formulation can be manufactured in the manner set forth above with regard to Example 2, with the components provided in the following amounts:

Composition	Amount (μg)	Percent
Apomorphine Hydrochloride	200	10
Lactose	1800	90
Total	2000	100

Example 12: Preparation of 200 microgram formulation in 1 Mg Blister

[0166] A 200 microgram formulation can be manufactured in the manner set forth above with regard to Example 2, with the components provided in the following amounts:

Composition	Amount (μg)	Percent
Apomorphine Hydrochloride	200	20
Lactose	800	80
Total	1000	100

Example 13: Preparation of 400 microgram formulation in 2 Mg Blister

[0167] A 400 microgram formulation can be manufactured in the manner set forth above with regard to Example 2, with the components provided in the following amounts:

Composition	Amount (μg)	Percent
Apomorphine Hydrochloride	400	20
Lactose	1600	80
Total	2000	100

[0168] In the preceding specification, the invention has been described with reference to specific exemplary embodiments and examples thereof. It will, however, be evident that various modifications and changes may be made thereto without departing from the broader spirit and scope of the invention as set forth in the claims that follow. The specification and drawings are accordingly to be regarded in an illustrative manner rather than a restrictive sense.

DDK Docket No. 478.1045

What is claimed is:

1. A method for treating sexual dysfunction via inhalation, comprising: inhaling a dose of a powder composition, the powder composition comprising apomorphine or pharmaceutically acceptable salts thereof.

2. The method of claim 1, wherein the powder composition further includes a carrier material, and wherein the carrier material has an average particle size of from about 40 to about 70 microns, and at least 90 percent of said apomorphine has a particle size of 5 microns or less.

3. The method of claim 1, wherein the sexual dysfunction is erectile dysfunction.

4. The method of claim 1, wherein the sexual dysfunction is female sexual dysfunction.

5. The method of claim 1, wherein the erectile dysfunction is organic.

6. The method of claim 1, wherein the dose comprises from about 100 micrograms to about 1000 micrograms of apomorphine or a pharmaceutically acceptable salt thereof.

7. The method of claim 2, wherein the carrier material is lactose and said apomorphine is apomorphine hydrochloride.

8. The method of claim 7, wherein the dose includes from about 100 to about 800 micrograms of said apomorphine hydrochloride.

9. The method of claim 9, wherein at least 99% of the apomorphine hydrochloride has a particle size of 5 microns or less.

10. A method for treating sexual dysfunction via inhalation, comprising: inhaling a dose of a powder composition, the dose of the powder composition comprising from about 100 micrograms to about 2000 micrograms of apomorphine or pharmaceutically acceptable salts thereof.

11. The method of claim 10, wherein the dose of the powder composition comprising from about 100 micrograms to about 1600 micrograms of apomorphine or pharmaceutically acceptable salts thereof.

12. The method of claim 10, wherein the dose of the powder composition comprising from about 100 micrograms to about 1000 micrograms of apomorphine or pharmaceutically acceptable salts thereof.

13. The method of claim 10, wherein the dose of the powder composition comprising from about 100 micrograms to about 800 micrograms of apomorphine or pharmaceutically acceptable salts thereof.

14. A method for treating sexual dysfunction via inhalation, comprising: inhaling a dose of a powder composition, the powder composition comprising apomorphine or pharmaceutically acceptable salts thereof and a carrier material, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less.

15. A dose comprising a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof.

16. A dose comprising a powder composition including a carrier material and

apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less.

17. A drug loaded blister comprising

a base having a cavity formed therein, the cavity containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof, the cavity having an opening which is sealed by a rupturable covering.

18. A drug loaded blister comprising

a base having a cavity formed therein, the cavity containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less, the cavity having an opening which is sealed by a rupturable covering.

19. A method for producing an inhalable aerosol of a powdered apomorphine composition, the method comprising:

entraining a powdered composition in a gas flow upstream from an inlet port of a vortex chamber having a substantially circular cross-section, the powder composition including from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof and a carrier material,

directing the gas flow through the inlet port into the vortex chamber in a tangential direction;

directing the gas flow through the vortex chamber so as to aerosolise the powder composition; and

directing the gas flow with the powder composition out of the vortex chamber in an axial direction through an exit port, wherein a velocity of the gas flow at a distance

of 300 mm outside of the exit port is less than a velocity of the gas flow at the inlet port.

20. A method for producing an inhalable aerosol of a powdered apomorphine composition, the method comprising:

entraining a powdered composition in a gas flow upstream from an inlet port of a vortex chamber having a substantially circular cross-section, the powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

directing the gas flow through the inlet port into the vortex chamber in a tangential direction;

directing the gas flow through the vortex chamber so as to aerosolise the powder composition; and

directing the gas flow with the powder composition out of the vortex chamber in an axial direction through an exit port, wherein a velocity of the gas flow at a distance of 300 mm outside of the exit port is less than a velocity of the gas flow at the inlet port.

21. The method as recited in claim 19, wherein at least 80% of the entrained powdered composition passes through the exit port within 500 ms after the gas flow is directed into the inlet port.

22. The method of claim 19, wherein the velocity of the gas flow at a distance of 50 mm outside of the exit port is less than the velocity of the gas flow at the inlet port.

23. The method of claim 19, wherein the gas flow upstream of the inlet port is generated by a source of pressurized gas.

24. A method for producing an inhalable aerosol of a powdered apomorphine composition, the method comprising:

entraining a powdered composition including agglomerated particles in a gas flow upstream from an inlet port of a vortex chamber, the agglomerated particles including about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof and a carrier material;

directing the gas flow through the inlet port into the vortex chamber;

depositing the agglomerated particles onto one or more walls of the vortex chamber;

applying, via the gas flow through the vortex chamber, a shear to the deposited agglomerated particles to deagglomerate said particles,

directing the gas flow, including the deagglomerated particles, out of the vortex chamber, wherein a velocity of the gas flow at a distance of 300 mm outside of the exit port is less than a velocity of the gas flow at the inlet port.

25. A method for producing an inhalable aerosol of a powdered apomorphine composition, the method comprising:

entraining a powdered composition including agglomerated particles in a gas flow upstream from an inlet port of a vortex chamber, the agglomerated particles including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

directing the gas flow through the inlet port into the vortex chamber;

depositing the agglomerated particles onto one or more walls of the vortex chamber;

applying, via the gas flow through the vortex chamber, a shear to the deposited agglomerated particles to deagglomerate said particles,

directing the gas flow, including the deagglomerated particles, out of the vortex chamber, wherein a velocity of the gas flow at a distance of 300 mm outside of the exit port is less than a velocity of the gas flow at the inlet port.

26. The method of claim 24, wherein the velocity of the gas flow at a distance of 50 mm outside of the exit port is less than the velocity of the gas flow at the inlet port.

27. The method of claim 24, wherein the gas flow upstream of the inlet port is generated by a source of pressured gas.

28. A method for producing an inhalable aerosol of a powered apomorphine composition, the method comprising:

entraining agglomerated particles in a gas flow, the agglomerated particles including a carrier material having an average particle size of from about 40 microns to about 70 microns and from about 100 to about 800 micrograms apomorphine or a pharmaceutically acceptable salt thereof, at least 90% of said apomorphine having a particle size of 5 microns or less.

depositing the agglomerated particles onto one or more surfaces;

applying, via the gas flow, a shear to the deposited agglomerated particles to deagglomerate said particles.

29. A method for producing an inhalable aerosol of a powered apomorphine composition , the method comprising:

entraining a powdered composition including agglomerated particles in a gas flow upstream from an inlet port of a vortex chamber, the agglomerated particles including a carrier material having an average particle size of from about 40 microns to about 70 microns and from about 100 to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

directing the gas flow through the inlet port into the vortex chamber;

depositing the agglomerated particles onto one or more walls of the vortex chamber;

applying, via the gas flow through the vortex chamber, a shear to the deposited agglomerated particles to deagglomerate said particles; and

directing the gas flow, including the deagglomerated particles, out of the vortex chamber.

30. A method of inhaling an aerosol of a powdered apomorphine composition, the method comprising:

generating an air flow through an inlet port of a chamber, the air flow having entrained therein a from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof and a carrier material ;

directing the air flow through the chamber, the chamber having an axis and a wall curved about the axis, the air flow rotating about the axis; and

directing the air flow through an exit port of the chamber,

wherein a direction of the air flow through the inlet port is tangential to the wall, and a direction of the air flow through the exit port is parallel to the axis,

and wherein a cross-sectional area of the air flow through the chamber is in a plane normal to the air flow and decreases with increasing distance from the inlet port.

31. A method of inhaling an aerosol of a powdered apomorphine composition, the method comprising:

generating an air flow through an inlet port of a chamber, the air flow having entrained therein a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

directing the air flow through the chamber, the chamber having an axis and a wall curved about the axis, the air flow rotating about the axis; and

directing the air flow through an exit port of the chamber,

wherein a direction of the air flow through the inlet port is tangential to the wall, and a direction of the air flow through the exit port is parallel to the axis,

and wherein a cross-sectional area of the air flow through the chamber is in a plane normal to the air flow and decreases with increasing distance from the inlet port.

32. An inhaler for producing an inhalable aerosol of a powdered apomorphine composition comprising

an aerosolising device in the form a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and a substantially axial exit port, wherein the ratio of the diameter of the vortex chamber to the diameter of the exit port is between 4 and 12;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

33. An inhaler for producing an inhalable aerosol of a powdered apomorphine composition comprising

an aerosolising device in the form a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and a substantially axial exit port, wherein the ratio of the diameter of the vortex chamber to the diameter of the exit port is between 4 and 12;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

34. An inhaler as claimed in claim 32, wherein the ratio is between 5 and 9.

35. An inhaler as claimed in claim 34, wherein the ratio is between 6 and 8.

36. An inhaler as claimed in claim 32, wherein the length of the exit port is less than the diameter of the exit port.

37. An inhaler for producing an inhalable aerosol of a powdered apomorphine composition comprising an aerosolising device in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port,

wherein the inlet port has an outer wall which defines the maximum extent of the inlet port in the radially outward direction of the vortex chamber,

the extent of the outer wall in the axial direction of the vortex chamber is substantially equal to the maximum extent of the inlet port in the axial direction of the vortex chamber, and

the outer wall is substantially parallel with a wall of the vortex chamber;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

38. An inhaler for producing an inhalable aerosol of a powdered apomorphine composition comprising an aerosolising device in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port,

wherein the inlet port has an outer wall which defines the maximum extent of the inlet port in the radially outward direction of the vortex chamber,

the extent of the outer wall in the axial direction of the vortex chamber is substantially equal to the maximum extent of the inlet port in the axial direction of the vortex chamber, and

the outer wall is substantially parallel with a wall of the vortex chamber;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the

carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

39. An inhaler as claimed in claim 37, wherein the vortex chamber comprises an exit port, preferably an axial exit port.

40. An inhaler as claimed in claim 37, wherein the outer wall of the inlet port is provided by the wall of the vortex chamber.

41. An inhaler as claimed in claim 37, wherein the inlet port is rectangular in cross-section.

42. An inhaler as claimed in claim 37, wherein the vortex chamber comprises a bottom surface which defines the furthest extent of the vortex chamber from the exit port in the axial direction, and the bottom surface further defines the furthest axial extent of the inlet port.

43. An inhaler for producing an inhalable aerosol of a powdered apomorphine composition comprising

an aerosolising device in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port, an exit port spaced from the inlet port in an axial direction, and a bottom surface which defines the furthest extent of the vortex chamber from the exit port in the axial direction, wherein the bottom surface further defines the furthest axial extent of the inlet port from the exit port,

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

44. An inhaler for producing an inhalable aerosol of a powdered apomorphine composition comprising

an aerosolising device in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port, an exit port spaced from the inlet port in an axial direction, and a bottom surface which defines the furthest extent of the vortex chamber from the exit port in the axial direction, wherein the bottom surface further defines the furthest axial extent of the inlet port from the exit port,

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

45. An inhaler for producing an inhalable aerosol of a powdered apomorphine composition comprising

an aerosolising device in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and an inlet conduit arranged to supply a powdered composition entrained in a gas flow to the inlet port, in use, wherein the cross-sectional area of the inlet conduit decreases towards the vortex chamber;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the inlet conduit with the powder composition in the received blister.

46. An inhaler for producing an inhalable aerosol of a powdered apomorphine composition comprising

an aerosolising device in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and an inlet conduit arranged to supply a powdered composition entrained in a gas flow to the inlet port, in use, wherein the cross-sectional area of the inlet conduit decreases towards the vortex chamber;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the inlet conduit with the powder composition in the received blister.

47. An inhaler as claimed in claim 45, wherein the inlet conduit comprises an outer wall which is substantially tangential to the vortex chamber at the inlet port and an inner wall which converges towards the outer wall in the direction towards the vortex chamber.

48. An inhaler for producing an inhalable aerosol of a powdered apomorphine composition comprising

an aerosolising device in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and an arcuate inlet conduit arranged to supply a powdered composition entrained in a gas flow to the inlet port, in use;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the inlet conduit with the powder composition in the received blister.

49. An inhaler for producing an inhalable aerosol of a powdered apomorphine composition comprising

an aerosolising device in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and an arcuate inlet conduit arranged to supply a powdered composition entrained in a gas flow to the inlet port, in use;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the inlet conduit with the powder composition in the received blister.

50. An inhaler as claimed in claim 48, wherein the inlet conduit is in the form of a spiral around the vortex chamber.

51. An inhaler comprising:

a chamber having a top portion, a bottom portion, and a substantially cylindrical center portion, the chamber having an inlet port tangential to the center portion, the top portion having an exit port, wherein a ratio of a diameter of the chamber to a diameter of the exit port is between 4 and 12;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

52. An inhaler comprising:

a chamber having a top portion, a bottom portion, and a substantially cylindrical center portion, the chamber having an inlet port tangential to the center portion, the top portion having an exit port, wherein a ratio of a diameter of the chamber to a diameter of the exit port is between 4 and 12;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

53. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising:

a chamber having a top portion, a bottom portion, and a cylindrical center portion, the chamber having an inlet port tangential to the cylindrical center portion, the chamber having an exit port in the top portion, wherein a length of the exit port is less than a diameter of the exit port;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

54. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising:

a chamber having a top portion, a bottom portion, and a cylindrical center portion, the chamber having an inlet port tangential to the cylindrical center portion, the chamber having an exit port in the top portion, wherein a length of the exit port is less than a diameter of the exit port;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

55. The inhaler as recited in claim 53, wherein the exit port is co-axial with a longitudinal axis of the cylindrical center portion.

56. The inhaler as recited in claim 55, wherein the inlet port is perpendicular to the longitudinal axis of the cylindrical center portion.

57. The inhaler as recited in claim 54, wherein the length of the exit port is less than half the diameter of the exit port.

58. The inhaler as recited in claim 53, wherein the top portion includes a wall, and wherein the exit port is defined as a passage through the wall, the wall being tapered towards the exit port so that the length of the exit port is less than a maximum thickness of the wall.

59. The inhaler as recited in claim 54, wherein the top portion includes a wall, the wall having a planar inner surface defining a furthest extent in an axial direction of the chamber from the inlet port.

60. The inhaler as recited in claim 53, wherein the inlet port intersects the chamber at an opening in the center portion, the opening extending along the center portion substantially from the bottom portion to the top portion.

61. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising

an aerosolising device having formed therein, a chamber of substantially circular cross-section, the chamber having a substantially planar top surface, a substantially planar bottom surface, and a curved lateral surface, the aerosolising device including an inlet port, the inlet port extending from an outer surface of the aerosolising device to the chamber, the inlet port being tangential to the curved lateral surface, the aerosolising device further including an outlet port, the outlet port extending from the outer surface of the aerosolising device to the planar top surface of the chamber;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

62. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising

an aerosolising device having formed therein, a chamber of substantially circular cross-section, the chamber having a substantially planar top surface, a substantially planar bottom surface, and a curved lateral surface, the aerosolising device including an inlet port, the inlet port extending from an outer surface of the aerosolising device to the chamber, the inlet port being tangential to the curved lateral surface, the aerosolising device further including an outlet port, the outlet port extending from the outer surface of the aerosolising device to the planar top surface of the chamber;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the

carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

63. The inhaler as recited in claim 61, wherein the inlet port intersects the chamber at an opening in the lateral surface, a height of the opening being at least half of a height of the lateral surface.

64. The inhaler as recited in claim 63, wherein the inlet port includes an upper wall segment, a lower wall segment, a first lateral wall segment, and a second lateral wall segment, the first lateral wall segment intersecting the chamber at an acute angle, a portion of the second lateral wall segment defining a portion of the lateral surface of the chamber.

65. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising

an aerosolising device defining a vortex chamber of substantially circular cross-section having a tangential inlet port, the aerosolising device including a vortex chamber wall defining a radially outer boundary of the vortex chamber and defining a maximum extent of the inlet port in a radially outward direction of the vortex chamber;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

66. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising

an aerosolising device defining a vortex chamber of substantially circular cross-section having a tangential inlet port, the aerosolising device including a vortex chamber wall defining a radially outer boundary of the vortex chamber and defining a maximum extent of the inlet port in a radially outward direction of the vortex chamber;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

67. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising:

an aerosolising device defining a vortex chamber of substantially circular cross-section having a tangential inlet port, an exit port spaced a distance apart from the inlet port in an axial direction, the aerosolising device including a vortex chamber bottom surface defining a furthest extent of the vortex chamber from the exit port in an axial direction and a furthest axial extent of the inlet port.

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

68. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising:

an aerosolising device defining a vortex chamber of substantially circular cross-section having a tangential inlet port, an exit port spaced a distance apart from the inlet port in an axial direction, the aerosolising device including a vortex chamber bottom

surface defining a furthest extent of the vortex chamber from the exit port in an axial direction and a furthest axial extent of the inlet port.

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

69. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising:

an aerosolising device defining a vortex chamber of substantially circular cross-section having a tangential inlet port; and

an inlet conduit arranged to supply a powdered composition entrained in a gas flow to the inlet port, wherein a cross-sectional area of the inlet conduit decreases towards the vortex chamber;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the inlet conduit with the powder composition in the received blister.

70. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising:

an aerosolising device defining a vortex chamber of substantially circular cross-section having a tangential inlet port; and

an inlet conduit arranged to supply a powdered composition entrained in a gas flow to the inlet port, wherein a cross-sectional area of the inlet conduit decreases towards the vortex chamber;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the inlet conduit with the powder composition in the received blister.

71. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising:

an aerosolising device defining a vortex chamber of substantially circular cross-section having a tangential inlet port; and

an arcuate inlet conduit arranged to supply the powdered composition entrained in a gas flow to the inlet port;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the inlet conduit with the powder composition in the received blister.

72. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising:

an aerosolising device defining a vortex chamber of substantially circular cross-section having a tangential inlet port; and

an arcuate inlet conduit arranged to supply a powdered composition entrained in a gas flow to the inlet port;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the inlet conduit with the powder composition in the received blister.

73. An inhaler for producing an inhalable aerosol of a powdered medicament comprising an aerosolising device in the form of a vortex chamber having an axis and being defined, at least in part, by a wall which forms a curve about the axis, the vortex chamber having a cross-sectional area in a plane bounded by the axis, the plane extending in one direction radially from the axis at a given angular position (θ) about the axis,

wherein the vortex chamber has a substantially tangential inlet port and a substantially axial exit port, and

said cross-sectional area of the vortex chamber decreases with increasing angular position (θ) in the direction, in use, of gas flow between the inlet port and the exit port;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

74. An inhaler for producing an inhalable aerosol of a powdered composition comprising an aerosolising device in the form of a vortex chamber having an axis and being defined, at least in part, by a wall which forms a curve about the axis, the vortex chamber having a cross-sectional area in a plane bounded by the axis, the plane extending in one direction radially from the axis at a given angular position (θ) about the axis,

wherein the vortex chamber has a substantially tangential inlet port and a substantially axial exit port, and

said cross-sectional area of the vortex chamber decreases with increasing angular position (θ) in the direction, in use, of gas flow between the inlet port and the exit port;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less; and

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

75. An inhaler as claimed in claim 73, wherein the distance (R) of the wall from the axis decreases with angular position (θ).

76. An inhaler as claimed in claim 74, wherein the distance (R) of the wall from the axis decreases with angular position (θ) substantially in accordance with the relationship $R = R_{max}\{1-f(\theta)\}$, where R_{max} is a maximum radius, $f(\theta)$ is a function of θ, $0 \leq f(\theta) < 1$ for $0 \leq \theta < 2\pi$ and $df/d\theta \geq 0$ for $0 < \theta < 2\pi$ and $df/d\theta > 0$ for at least some of the range $0 \leq \theta < 2\pi$.

77. An inhaler as claimed in claim 76, wherein $df/d\theta > 0$ for substantially the whole range $0 \leq \theta < 2\pi$.

78. An inhaler as claimed in claim 76, wherein $df/d\theta$ is a constant (k) for at least some of the range $0 \leq \theta < 2\pi$.

79. An inhaler as claimed in claim 78, wherein $f(\theta)$ is substantially given by $f(\theta) = \theta(k/2\pi)$, where k is a constant and $0 < k < 1$.

80. An inhaler as claimed in claim 78, wherein $5\% < k < 50\%$, preferably $10\% < k < 25\%$.

81. An inhaler as claimed in claim 73, wherein the vortex chamber is further defined by a base and a roof, and the distance (H) between the base and the roof decreases with angular position (θ).

82. An inhaler as claimed in claim 81, wherein the distance (H) between the base and the roof decreases with angular position (θ) substantially in accordance with the relationship $H = H_{max}\{1-g(\theta)\}$, where H_{max} is a maximum height, $g(\theta)$ is a function of θ, $0 \leq g(\theta) < 1$ for $0 \leq \theta < 2\pi$ and $dg/d\theta \geq 0$ for $0 < \theta < 2\pi$ and $dg/d\theta > 0$ for at least some of the range $0 \leq \theta < 2\pi$.

83. An inhaler as claimed in claim 82, wherein $g(\theta)$ is substantially zero for $0 \leq \theta < \theta_1$ where θ_1 is a constant and $dg/d\theta > 0$ for at least some of the range $\theta_1 \leq \theta < 2\pi$.

84. An inhaler as claimed in claim 82, wherein $g(\theta)$ for the range of values of $\theta_1 \leq \theta < \theta_{max}$ is substantially given by $g(\theta) = j(\theta - \theta_1)/(\theta_{max} - \theta_1)$, where j is a constant and $0 < j < 1$.

85. An inhaler as claimed in claim 84, wherein $25\% < j < 50\%$, preferably $40\% < j < 60\%$.

86. An inhaler as claimed in claim 73, wherein the vortex chamber is further defined by a base, and the distance (d) between the base and a plane which is normal to the axis and is located on the opposite side of the base to the exit part increases with radial position (r) relative to the axis.

87. An inhaler for producing an inhalable aerosol of a powdered composition comprising

an aerosolising device in the form of a vortex chamber having an axis and being defined, at least in part, by a wall which forms a curve about the axis, the vortex chamber having a substantially tangential inlet port and a substantially axial exit port,

wherein the vortex chamber is further defined by a base, and the distance (d) between the base and a plane which is normal to the axis and is located on the opposite side of the base to the exit port increases with radial position (r) relative to the axis;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

88. An inhaler for producing an inhalable aerosol of a powdered composition comprising

an aerosolising device in the form of a vortex chamber having an axis and being defined, at least in part, by a wall which forms a curve about the axis, the vortex chamber having a substantially tangential inlet port and a substantially axial exit port, wherein the vortex chamber is further defined by a base, and the distance (d) between the base and a plane which is normal to the axis and is located on the opposite side of the base to the exit port increases with radial position (r) relative to the axis;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

89. An inhaler as claimed in claim 87, wherein the distance (d) between the base and the normal plane increased with radial position (r) substantially in accordance with the relationship $d = d_{max}\, e(r)$, where d_{max} is a maximum distance e(r) is a function of r, $0 \leq e(r) < 1$ for $0 \leq r \leq R_{max}$ and $de/dr \geq 0$ for $0 \leq r \leq R_{max}$ and $de/dr > 0$ for at least some of the range $0 \leq r \leq R_{max}$.

90. An inhaler as claimed in claim 89, wherein e(r) is substantially zero for $0 \leq r < r_1$ where r_1 is a minimum radius and $de/dr > 0$ for at least some of the range $r_1 \leq r \leq R_{max}$.

91. An inhaler as claimed in claim 89, wherein e(r) for the range of values of $r_1 \leq r \leq R_{max}$ is substantially given by $e(r) = m(r - r_1)/(R_{max} - r_1)$, where m is a constant and $0 < m < 1$.

92. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising:

a chamber defined by a top wall, a bottom wall, and a lateral wall, the lateral wall being curved about an axis which intersects the top wall and the bottom wall, the chamber enclosing a cross-sectional area defined by the axis, the top wall, the bottom wall and the lateral wall;

the chamber having an inlet port and an outlet port, the inlet port being tangent to the lateral wall, the outlet port being co-axial with the axis, the cross-sectional area decreasing with increasing angular position from the inlet port in a direction of a gas flow through the inlet port;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

93. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising:

a chamber defined by a top wall, a bottom wall, and a lateral wall, the lateral wall being curved about an axis which intersects the top wall and the bottom wall, the chamber enclosing a cross-sectional area defined by the axis, the top wall, the bottom wall and the lateral wall;

the chamber having an inlet port and an outlet port, the inlet port being tangent to the lateral wall, the outlet port being co-axial with the axis, the cross-sectional area decreasing with increasing angular position from the inlet port in a direction of a gas flow through the inlet port;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

94. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising:

a chamber including a wall, a base, an inlet port and an exit port, the chamber having an axis that is co-axial with the exit port and intersects the base, the wall being curved about the base, the inlet port being tangential to the wall, a height between the base and a plane normal to the axis at the exit port decreasing as a radial position from the axis to the inlet port increases;

one or more sealed blisters, each blister containing a powder composition including a carrier material and from about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

95. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising:

a chamber including a wall, a base, an inlet port and an exit port, the chamber having an axis that is co-axial with the exit port and intersects the base, the wall being curved about the base, the inlet port being tangential to the wall, a height between the

base and a plane normal to the axis at the exit port decreasing as a radial position from the axis to the inlet port increases;

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof, the carrier material having an average particle size of from about 40 to about 70 microns, at least 90 percent of said apomorphine having a particle size of 5 microns or less;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the tangential inlet port with the powder composition in the received blister.

96. The inhaler as recited in claim 94, wherein the height (H) between the base and the roof is given substantially by $H = H_{max}\{1-e(r)\}\times\{1-g(\theta)\}$, wherein r is the radial position from the axis.

97. An inhaler as claimed in claim 81, wherein the distance (H) between the base and the roof decreases with angular position (θ) substantially in accordance with the relationship $H = H_{max}\{1-g(\theta)\}$, where H_{max} is a maximum height, r is the radial position from the axis $g(\theta)$ is a function of θ, $0 \le g(\theta) < 1$ for $0 \le \theta < 2\pi$ and $dg/d\theta \ge 0$ for $0 < \theta < 2\pi$ and $dg/d\theta > 0$ for at least some of the range $0 \le \theta < 2\pi$, (r) is a function of r, $0 \le e(r) < 1$ for $0 \le r \le R_{max}$ and $de/dr \ge 0$ for $0 \le r \le R_{max}$ and $de/dr > 0$ for at least some of the range $0 \le r \le R_{max}$.

98. The method of claim 1, wherein the powder composition includes a force control additive and a carrier.

99. The method of claim 98, wherein the force control additive is provided in an amount from about 0.1% to about 10% of the carrier material, by weight.

100. The method of claim 99, wherein the force control additive is selected from the group consisting of magnesium stearate, leucine, lecithin, and sodium stearyl fumarate.

101. The blister of claim 17, wherein the base and the rupturable covering are made of foil.

102. The blister of claim 17, wherein the base is made of a polymer and the rupturable covering is made of foil

103. The blister of claim 18, wherein the base and the rupturable covering are made of foil.

104. The blister of claim 18, wherein the base is made of a polymer and the rupturable covering is made of foil

105. The blister of claim 17, wherein the powder composition comprises about 1 mg of powder.

106. The blister of claim 17, wherein the powder composition comprises about 2 mg of powder.

107. The blister of claim 17, wherein the powder composition comprises about 3 mg of powder

108. The blister of claim 18, wherein the powder composition comprises about 1 mg of powder.

109. The blister of claim 18, wherein the powder composition comprises about 2 mg of powder.

110. The blister of claim 18, wherein the powder composition comprises about 3 mg of powder.

111. The blister of claim 17 or 18, wherein the powder composition comprises from about 3 % to about 80 % apomorphine or its pharmaceutically acceptable salts.

112. The blister of claim 111, wherein the powder composition comprises from about 5 % to about 30 % apomorphine or its pharmaceutically acceptable salts.

113. The blister of claim 111, wherein the powder composition comprises from about 5 % to about 20 % apomorphine or its pharmaceutically acceptable salts.

114. An inhaler for producing an inhalable aerosol of a powdered composition, the inhaler comprising:

a chamber having an inlet port and an outlet port, the outlet port coupled to a mouthpiece, the inlet port coupled to an inlet conduit,

one or more sealed blisters, each blister containing a powder composition including a carrier material and apomorphine or a pharmaceutically acceptable salt thereof;

an input for removably receiving one of the blisters, said inhaler, upon actuation, coupling the inlet conduit with the powder composition in the received blister.

115. The inhaler of claim 114, wherein the composition further includes a force control additive.

116. The inhaler of claim 115, wherein the inlet conduit terminates in a piercing rod, and wherein, upon actuation, the piercing rod pierces a covering of the received blister.

117. The inhaler of claim116, further comprising a source of compressed gas coupled to the received blister, the source of compressed gas effectuating movement of the powder composition from the received blister to the chamber via the inlet conduit.

118. The inhaler of claim 116, wherein the inhaler is a passive inhaler device.

119. The inhaler of claim 116, wherein the inhaler is an active inhaler device.

120. The inhaler of any one of claim 118, wherein the powder composition includes a force control additive and a carrier.

121. The inhaler of claim 120, wherein the force control additive is provided in an amount from about 0.15% to about 5% of the composition, by weight.

122. The method of claim 117, wherein the force control additive is selected from the group consisting of magnesium stearate, leucine, lecithin, and sodium stearyl fumarate.

123. The inhaler of claim 31, further comprising a source of compressed gas coupled to the received blister.

124. A drug loaded blister comprising

a base having a cavity formed therein, the cavity containing a powder composition including about 100 micrograms to about 800 micrograms of apomorphine or a pharmaceutically acceptable salt thereof, the cavity having an opening which is sealed by a rupturable covering.

DDK Docket No. 478.1045

ABSTRACT OF THE DISCLOSURE

A composition, device, and method for treating sexual dysfunction via inhalation is provided which comprises inhaling a dose of a powder composition, the powder composition comprising apomorphine or pharmaceutically acceptable salts thereof. Preferably, the powder composition further includes a carrier material, the carrier material has an average particle size of from about 40 to about 70 microns, and at least 90 percent of said apomorphine has a particle size of 5 microns or less.

DECLARATION AND POWER OF ATTORNEY

Docket No.: 478.1045US

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled:

COMPOSITION, DEVICE, AND METHOD FOR TREATING SEXUAL DYSFUNCTION VIA INHALATION,

the specification of which (check one).

☐ is attached hereto

☐ was filed on as Application Serial No. and was amended on .

☒ I hereby authorize and request our attorneys, Davidson, Davidson & Kappel, LLC of 485 Seventh Avenue, New York, New York 10018 to insert here in parentheses (application number _____, filed _____) the filing date and application number of said application when known.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information that is known to me to be material to the patentability of this application as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign and/or provisional application(s) for patent or inventor's certificate listed below and have also identified below any foreign and/or provisional application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Number	Country	Day/Month/Year Filed	Priority claimed ☐ Yes ☐ No
Number	Country	Day/Month/Year Filed	Priority claimed ☐ Yes ☐ No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial Number	Day/Month/Year Filed	Status
Application Serial Number	Day/Month/Year Filed	Status

And I hereby appoint Clifford M. Davidson, Reg. No. 32,728, Leslye B. Davidson, Reg. No. 38,854, Cary S. Kappel, Reg. No. 36,561, William C. Gehris, Reg. No. 38,156, Morey B. Wildes, Reg. No. 36,968, Robert J. Paradiso, Reg. No. 41,240, Erik R. Swanson, Reg. No. 40,833, Thomas P. Canty, Reg. No. 44,586, Livia S. Boyadjian, Reg. No. 34,781, and all other registered attorneys and agents at Davidson, Davidson & Kappel, LLC, U.S. Patent and Trademark Office Customer Number 23280, my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith; correspondence address: DAVIDSON, DAVIDSON & KAPPEL, LLC, 485 Seventh Avenue, 14th Floor, New York, New York 10018; Telephone: (212) 736-1940; Fax: (212) 736-2427.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code, §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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☒ Additional inventors named on attached sheet(s).

DECLARATION AND POWER OF ATTORNEY

Docket No.: 478.1045US

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Inventor's signature	
Date	
Residence	
Post Office Address	
Citizenship	

Full name of additional Inventor	
Inventor's signature	
Date	
Residence	
Post Office Address	
Citizenship	

Full name of additional Inventor	
Inventor's signature	
Date	
Residence	
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Citizenship	

Full name of additional Inventor	
Inventor's signature	
Date	
Residence	
Post Office Address	
Citizenship	

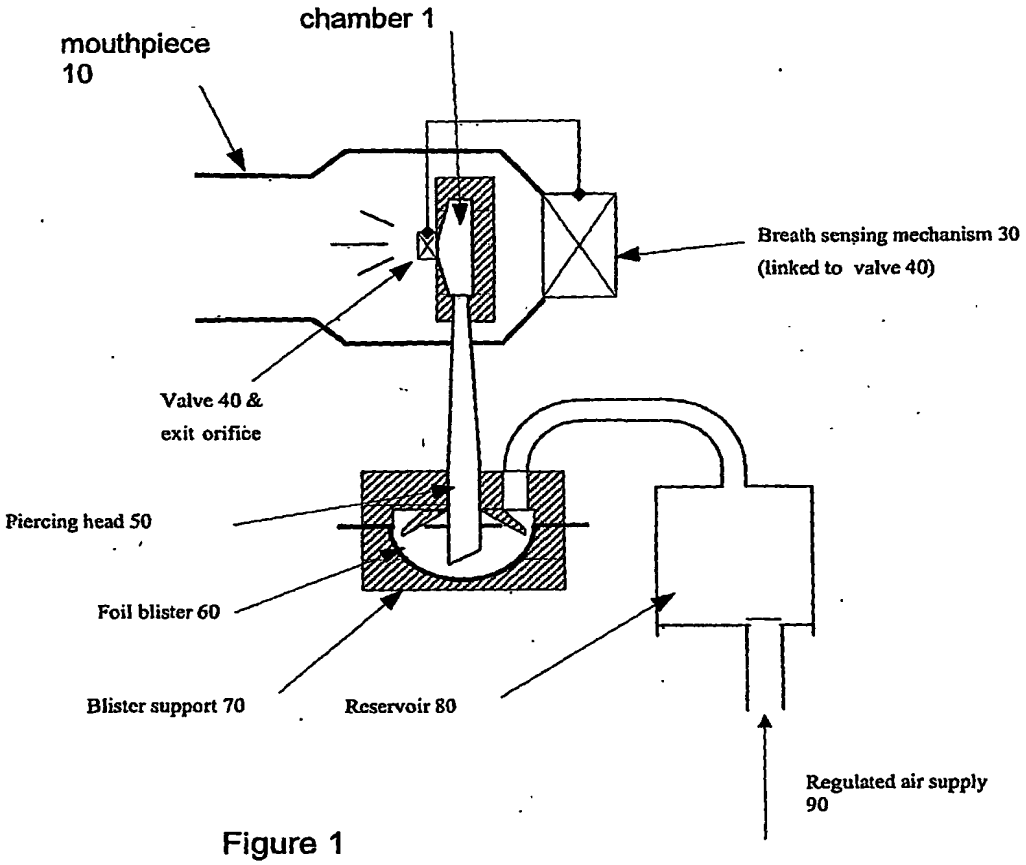

chamber 1
mouthpiece
10
Breath sensing mechanism 30
(linked to valve 40)
Valve 40 &
exit orifice
Piercing head 50
Foil blister 60
Blister support 70
Reservoir 80
Regulated air supply
90

Figure 1

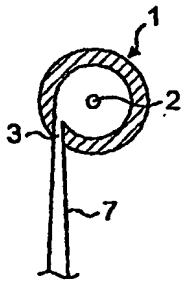


FIG. 2

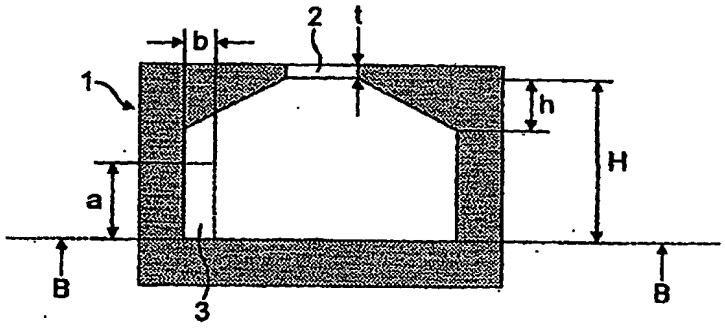


FIG. 3

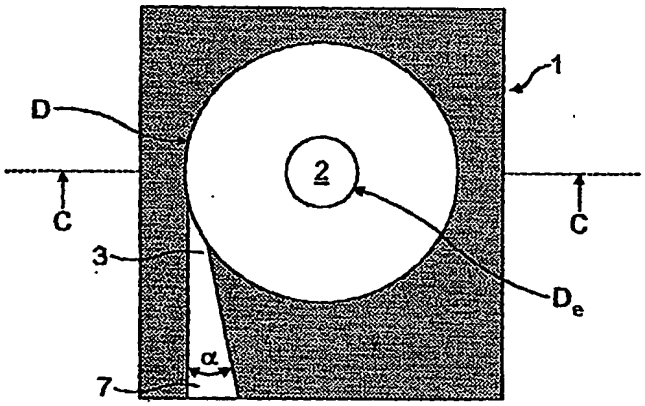


FIG. 4

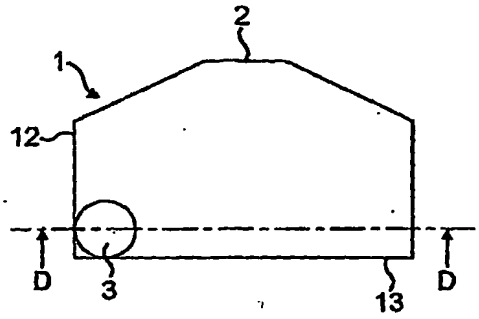


Figure 5a

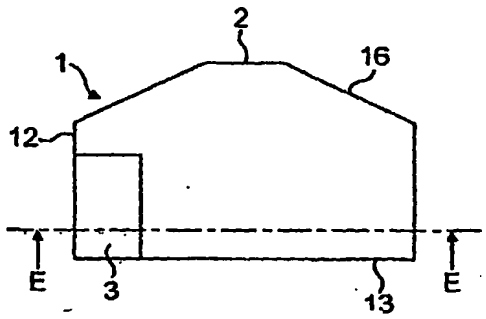


Figure 6a

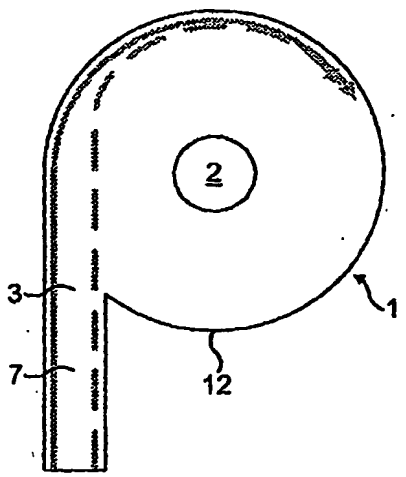


Figure 5b

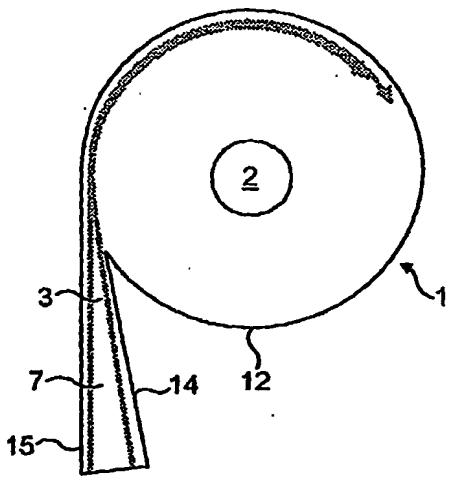


Figure 6b

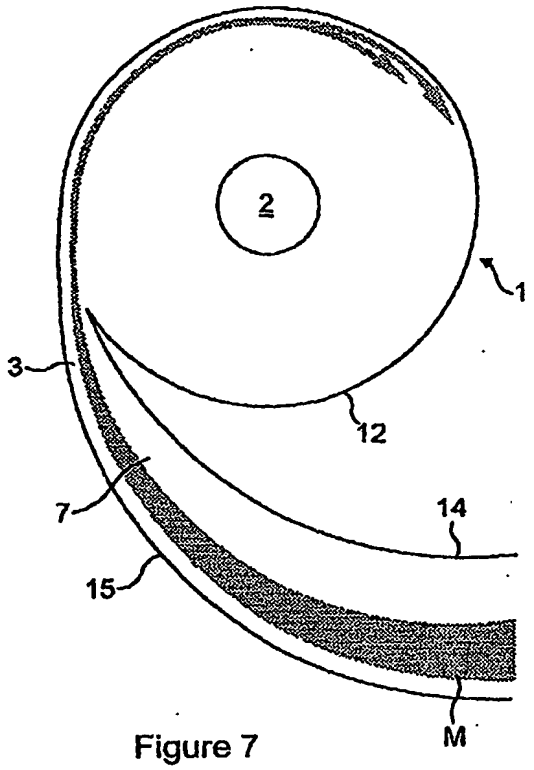


Figure 7

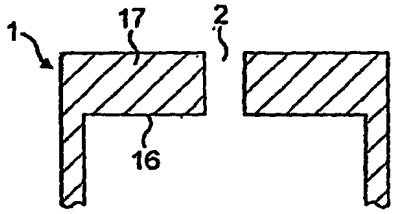


Figure 8

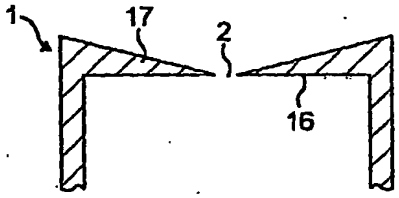


Figure 9

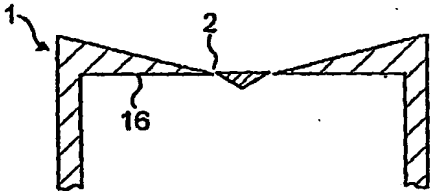


Figure 10

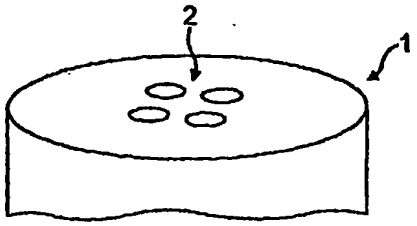


Figure 11

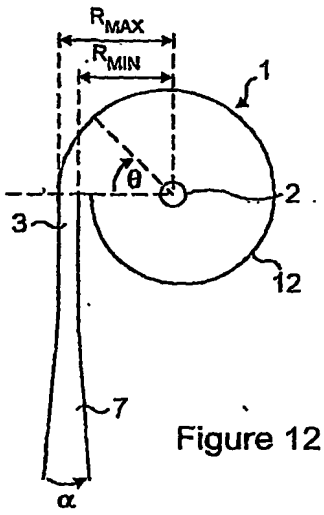


Figure 12

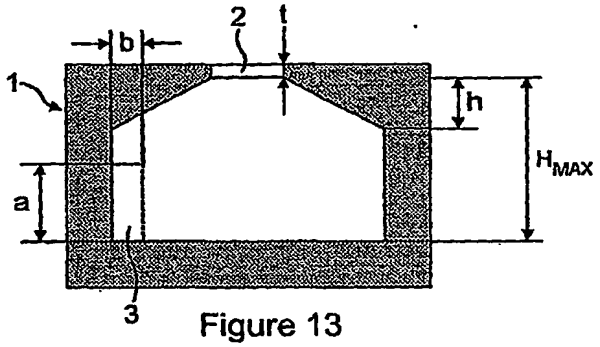


Figure 13

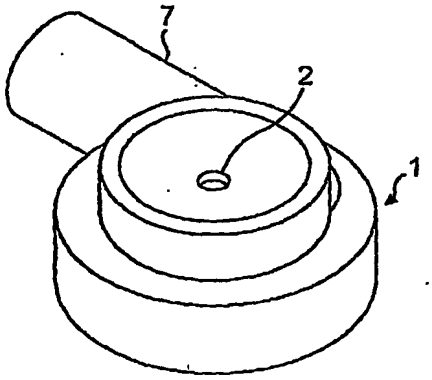


Figure 14

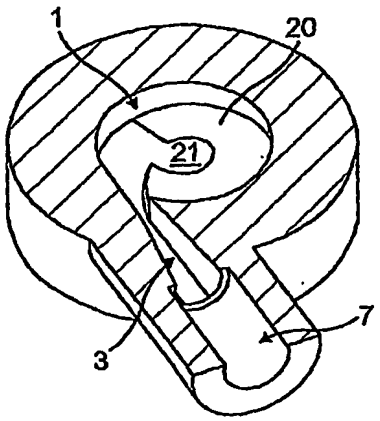


Figure 15

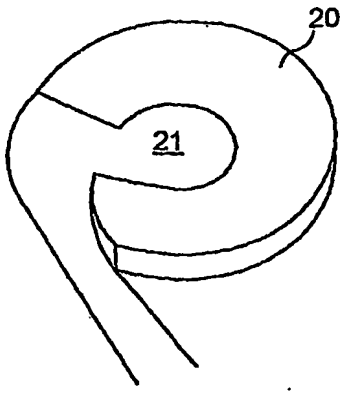


Figure 16

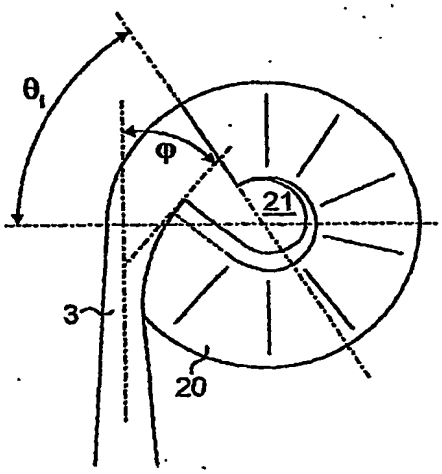


Figure 17

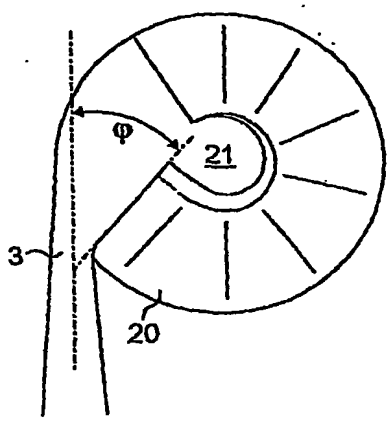


Figure 18

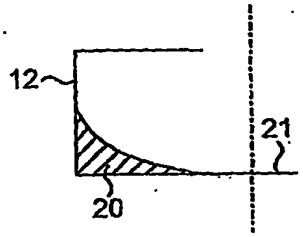


Figure 19

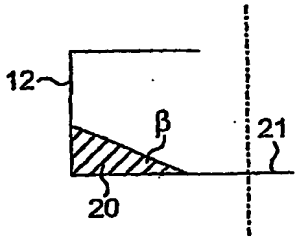


Figure 20

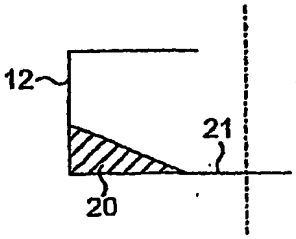


Figure 21

Figure 24

Stability Condition	Formulation	Assay - Initial	Rel subs (highest Indiv peak%) - Initial	Rel subs (sum of rel peaks)-Initial
Initial	Batch1	ND	0.03	0.7
	Batch2	ND	0.04	0.10
	Batch3	101	0.03	0.07
	Batch4	101	0.04	0.09
25 °C/60% RH	Formulation	Assay - 1 month	Rel subs (highest Indiv peak%) - 1 month	Rel subs (sum of rel peaks) - month
	Batch1	99	0.04	0.10
	Batch2	99	0.06	0.20
	Batch3	99	0.05	0.20
	Batch4	98	0.05	0.14
40 °C/75% RH	Formulation	Assay - 1 month	Rel subs (highest Indiv peak%) - 1 month	Rel subs (sum of rel peaks) - month
	Batch1	98	0.04	0.14
	Batch2	100	0.08	0.20
	Batch3	99	0.04	0.14
	Batch4	98	0.13	0.28

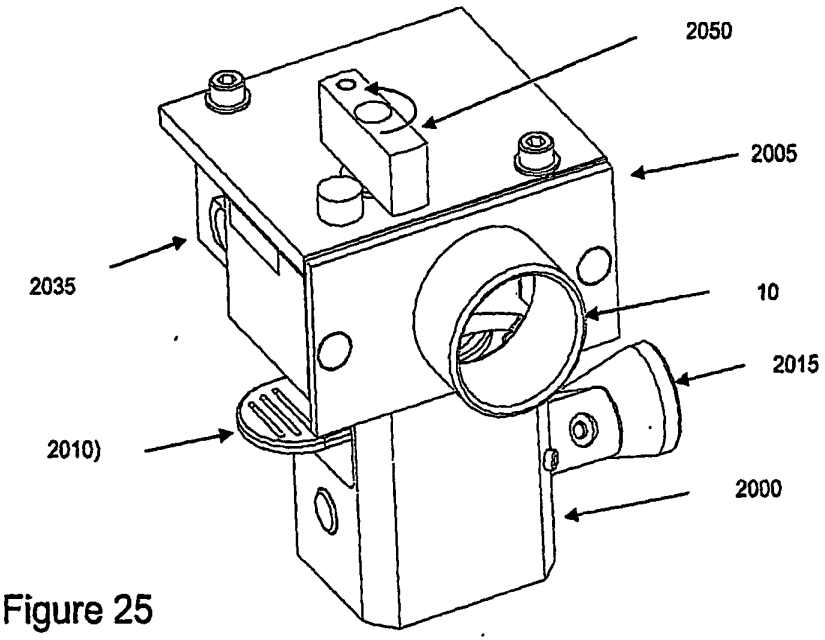


Figure 25

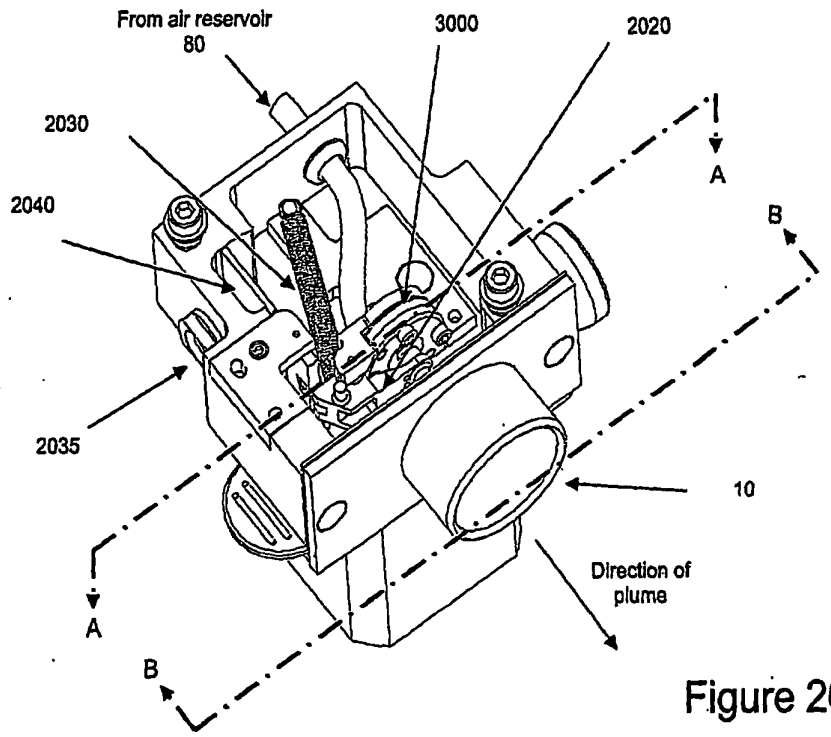


Figure 26

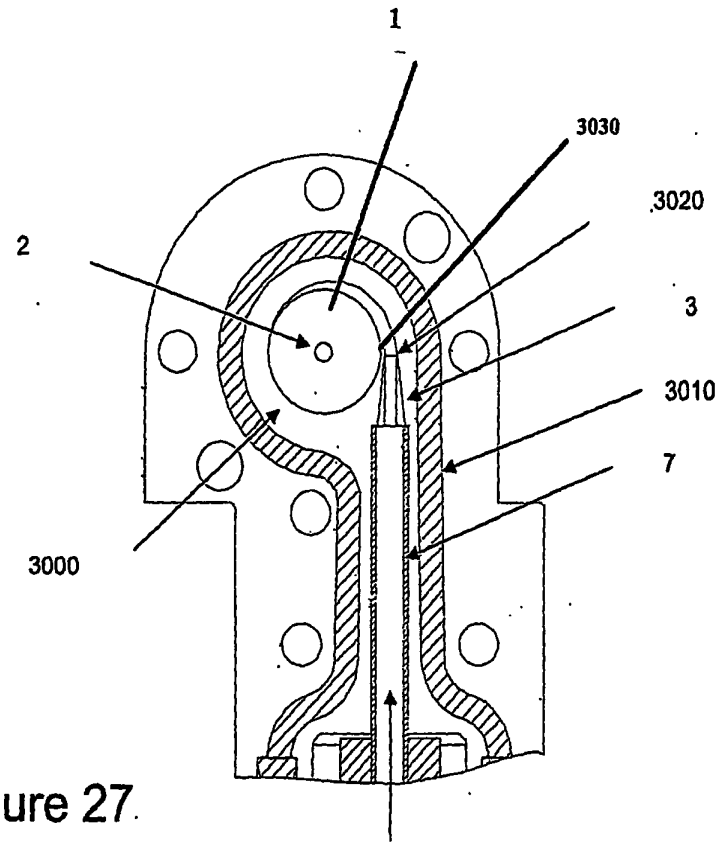

1
3030
3020
2
3
3010
7
3000
From drug storage blister
(not shown)

Figure 27.

Figure 28A

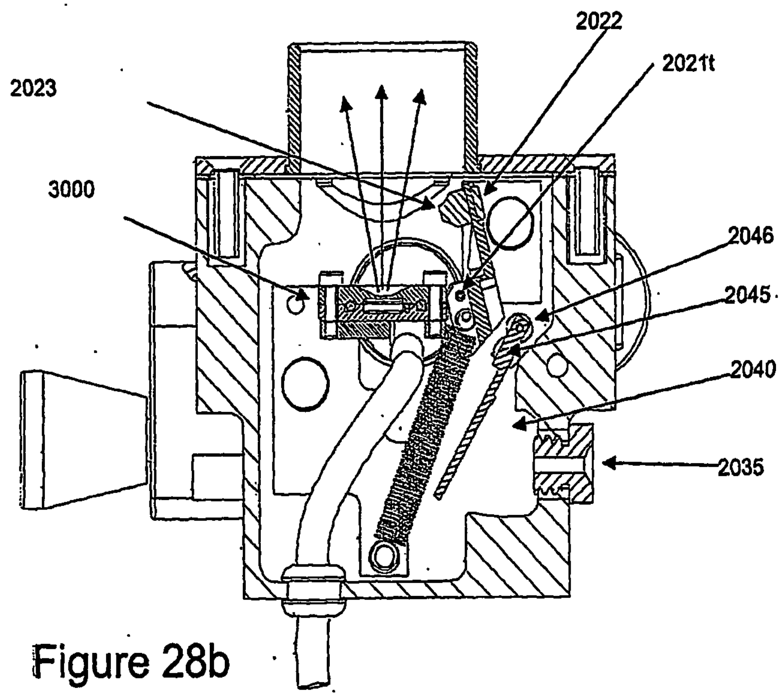


Figure 28b

Figure 29A

Formulation Details 5000	Uniformity of Delivered Dose 6000 (DUSA, n=10)					Fine Particle Performance (<5 µm Cut-Off) 7000 MSLI (ACI)								
	Drug Retention 6010		6015 DD (µg)	6020 Metered (µg)	6025 Mass Balance (%)	7005 n=	Drug Retention 7010		7015 DD (µg)	7020 FPD (µg)	7025 FPF (%)	7030 Metered	7035 Mass Balance (%)	7036 Test Flow Rate (L min^{-1})
	Blister (µg) 6012	Device (µg) 6013					Blister (µg) 6012	Device (µg) 6013						
100 µg 45 - 63 µm Inversina	7.2	4.3	84	95	93	3 (1)	7.7 (7.5)	7.5 (7.2)	85 (76)	56 (52)	66 (68)	100 (91)	95 (88)	95 (95)
100 µg 5 - 63 µm Air Jet Inversina	7.3	3.6	85	95	92	3	4.4	5.7	82	55	66	92	89	95
100 µg 45-63 µm Grindomix	Not Done					3	6.9	8.6	78	39	50	93	94	95
100 µg 30 - 63 µm Air Jet Grindomix	Not Done					3	5.4	6.3	86	40	47	97	96	95
100 µg 45 - 63 µm Air Jet Grindomix	Not Done					3	4.2	9.4	83	52	62	97	92	95
200 µg UF020100MGA 45 - 63 µm Air Jet Inversina	10.0	5.3	188	203	96	(2)	(7.8)	(14.5)	(175)	(122)	(70)	(197)	(94)	60

Figure 29B

Formulation Details 5000	Uniformily of Delivered Dose 6000 (DUSA, n=11)					Fine Particle Performance (<5 µm Cut-Off) 7000 MSLI(n=2)							
	Drug Retention 6010		Delivered Dose 6015		Metered Dose 6020 (µg)	Mass Balance 6025 (%)	Drug Retention 7010		Delivered Dose µg 7015	Fine Particle		Metred (µg)	Mass Balance (%)
	Blister (µg) 6012	Device (µg) 6013	(µg) 6016	% nominal 6017			Blister (µg) 6012	Device (µg) 7013		FPD (µg) 7020	FPF (%) 7505	7030	7035
100 µg 45 - 63 µm Inversina	6.6	7.8	81	81	95	95	8.8	5.6	82	52	64	96	96
200 µg 45 - 63 µm t Inversina	12.1	11.5	170	85	194	93	9.8	13.3	175	118	67	198	96
200 µg 45-63 µm Inversina	9.2 14.5	12.7 8.6	162 169	81 85	184 192	93 96	6.5	15.2	170	105	62	192	96
200 µg 45 - 63 µm Inversina	11.0	11.2	171	85	193	95	10.7	14.1	172	117	68	196	96

Test Flow Rate = 60 L Min^{-1}

Sample Name:
Micronised L-leucine

Sample Source:
Micronacnazzano
Sample batch number:
MM0001

Particle Name: Leucine			Accessory Name: Hydro 2000SM (A)			Obscuration:	7.96 %
Particle: 1.345 Absorption: 1.5			Analysis model: General purpose			Obscuration (blue):	9.29 %
Dispersant: Cyclohexane			Dispersant RI: 1.426			Weighted Residual:	0.422 %
Vol. Weighted Mean D[4,3]:	3.405 µm		Mode:	2.853 µm		Specific Surface Area:	2.38 m²/g
Surface Weighted Mean D[3,2]:	2.521 µm		Span:	1.487		Concentration:	0.0025 %Vol
Result units: Volume			Uniformity:	0.494			
d(0.1): 1.442 µm		d(0.5): 2.906 µm			D(0.90): 5.34 µm		d(0.9): 5.785 µm

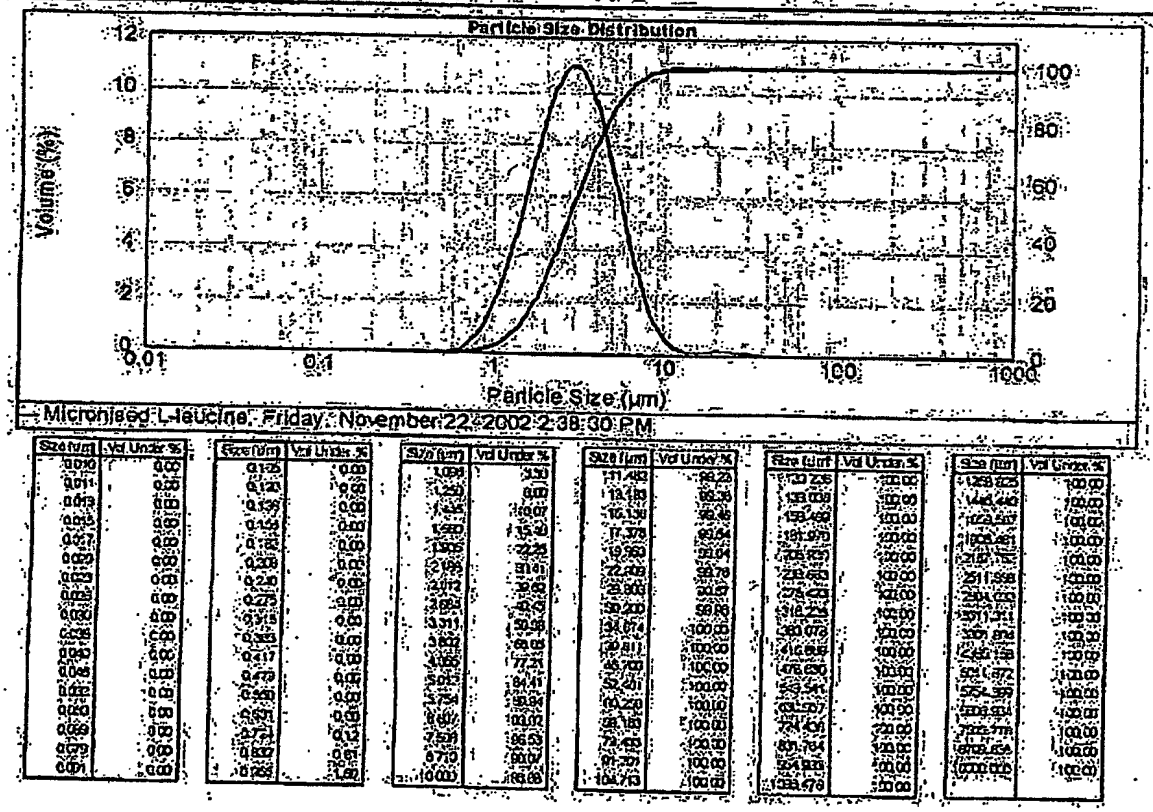


Figure 30

MASTERSIZER 2000

Result Analysis Report

Sample Name:
Respitose 45 - 63 µm

Particle Name:	Lactose	Accessory Name:	Hydro 2000SM (A)	Obscuration:	10.11 %
Particle RI:	1.347 Absorption: 0.1	Analysis model:	General purpose	Obscuration (blue):	6.69 %
Dispersant:	Cyclohexane	Dispersant RI:	1.426	Weighted Residual:	0.922 %
Vol. Weighted Mean D[4,3]:	53.494 µm	Mode:	59.194 µm	Specific Surface Area:	0.504 m²/g
Surface Weighted Mean D[3,2]:	11.916 µm	Span:	1.676	Concentration:	0.0247 %Vol
Result units:	Volume	Uniformity:	0.462		
d(0.1):	5.208 µm	d(0.5):	52.758 µm	d(0.9):	89.671 µm

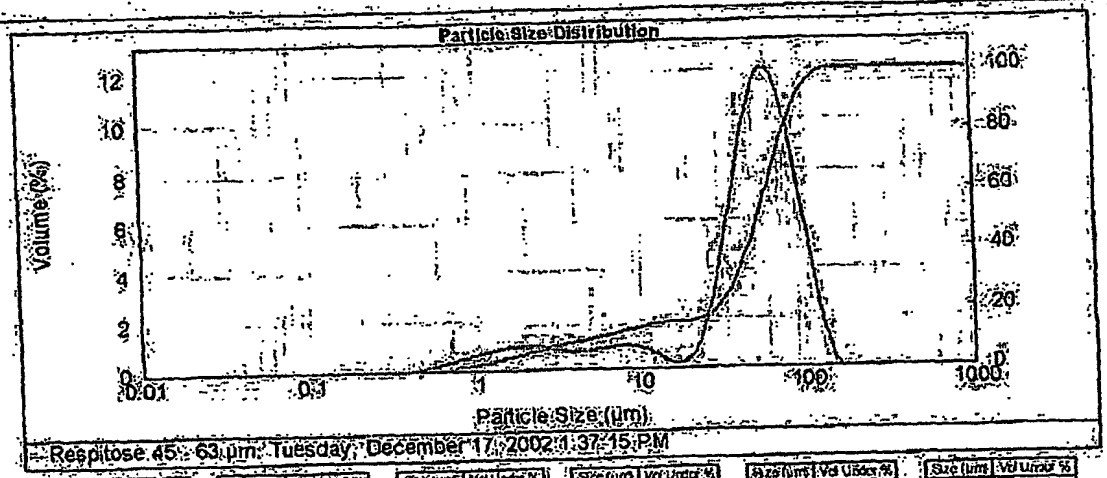


Figure 22(a)

10413022 .041403

MASTERSIZER 2000

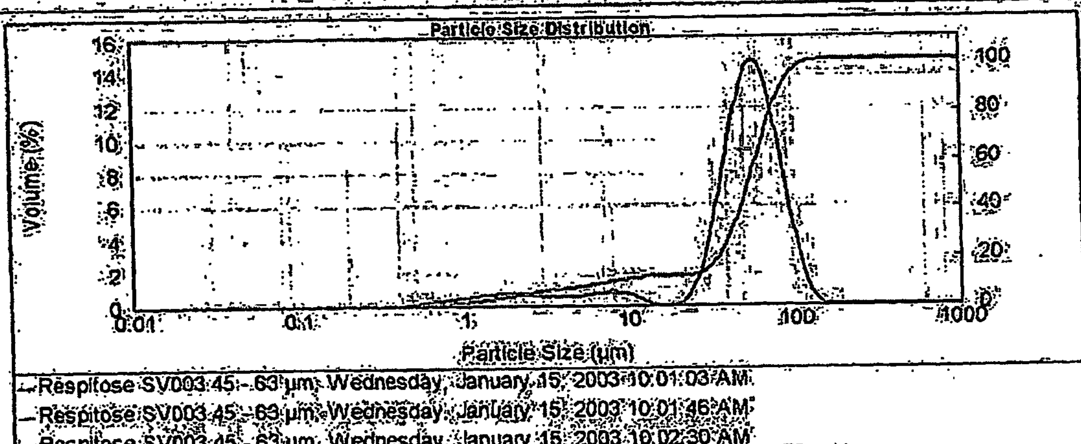
Result Analysis Report

Sample Name:
Respitose SV003 45 - 63 µm

Particle Name:	Lactose	Accessory Name:	Hydro 2000SM (A)	Obscuration:	12.22 %
Particle RI: 1.347	Absorption: 0.1	Analysis model:	General purpose	Obscuration (blue):	7.33 %
Dispersant:	Cyclohexane	Dispersant RI:	1.426	Weighted Residual:	0.627 %

Vol. Weighted Mean D[4,3]:	53.816 µm	Mode:	57.308 µm	Specific Surface Area:	0.41 m²/g
Surface Weighted Mean D[3,2]:	14.626 µm	Span:	1.464	Concentration:	0.0361 %Vol
Result units:	Volume	Uniformity:	0.384		

d(0.1): 8.871 µm   d(0.5): 53.882 µm   D(0.60): 59.64 µm   d(0.9): 97.148 µm



Size (µm)	Vol Under %
0.010	0.00
0.011	0.00
0.013	0.00
0.015	0.00
0.017	0.00
0.020	0.00
0.023	0.00
0.026	0.00
0.030	0.00
0.035	0.00
0.040	0.00
0.046	0.00
0.052	0.00
0.060	0.00
0.069	0.00
0.079	0.00
0.091	0.00

Size (µm)	Vol Under %
0.105	0.00
0.120	0.00
0.138	0.00
0.158	0.00
0.182	0.00
0.209	0.00
0.240	0.00
0.275	0.00
0.316	0.00
0.363	0.00
0.417	0.00
0.479	0.00
0.550	0.03
0.631	0.19
0.724	0.37
0.832	0.58
0.955	0.80

Size (µm)	Vol Under %
1.096	1.40
1.259	1.66
1.445	2.44
1.660	3.05
1.905	3.70
2.188	4.36
2.512	4.98
2.884	5.56
3.311	6.07
3.802	6.54
4.365	7.01
5.012	7.50
5.754	8.04
6.607	8.57
7.586	9.33
8.710	10.03
10.000	10.75

Size (µm)	Vol Under %
11.482	11.27
13.183	11.53
15.136	11.60
17.378	11.60
19.953	11.60
22.909	11.73
26.303	12.47
30.200	14.50
34.674	18.68
39.811	25.58
45.709	35.59
52.481	47.85
60.256	61.15
69.183	73.90
79.433	84.40
91.201	92.18
104.713	98.92

Size (µm)	Vol Under %
120.226	99.21
138.038	[illegible]
158.489	100.00
181.970	100.00
208.930	100.00
239.883	100.00
275.423	100.00
316.228	100.00
363.078	100.00
416.869	100.00
478.630	100.00
549.541	100.00
630.957	100.00
724.436	100.00
831.764	100.00
954.993	100.00
1096.478	100.00

Size (µm)	Vol Under %
1258.925	100.00
1445.440	100.00
1659.587	100.00
1905.461	100.00
2187.762	100.00
2511.886	100.00
2884.032	100.00
3311.311	100.00
3801.894	100.00
4365.158	100.00
5011.872	100.00
5754.399	100.00
6606.934	100.00
7585.776	100.00
8709.636	100.00
10000.000	100.00

Figure 22(b)

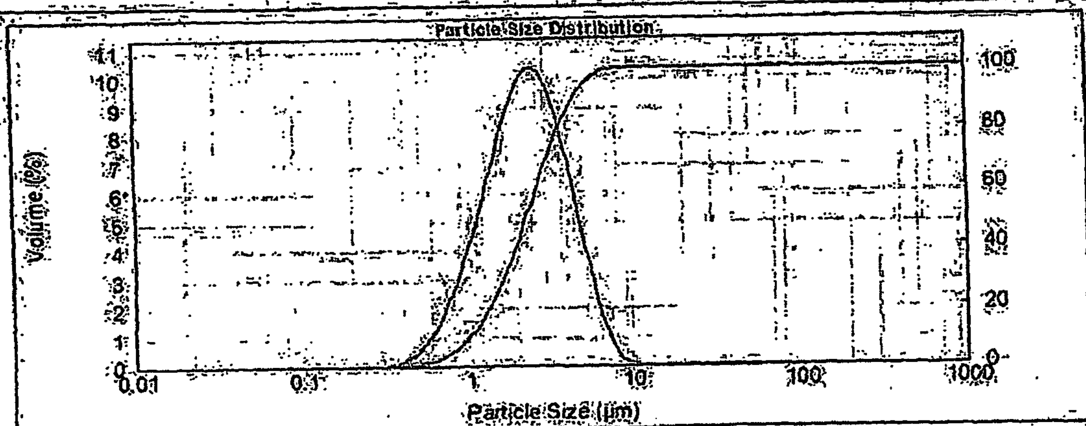
10413022 .041403

MASTERSIZER 2000

Result Analysis Report

Particle Name: VR004		Accessory Name: Hydro 2000SM (A)		Obscuration:		15.83	%
Particle RI: 3.000	Absorption: 0.05	Analysis model:	General purpose	Obscuration (blue):		15.22	%
Dispersant:	Cyclohexane	Dispersant RI:	1.426	Weighted Residual:		0.752	%

Vol. Weighted Mean D[4,3]:	2.587	µm	Mode:	2.468	µm	Specific Surface Area:	3.19 m²/g
Surface Weighted Mean D[3,2]:	1.880	µm	Span:	1.539		Concentration:	0.0088 %Vol
Result units:	Volume		Uniformity:	0.479			
d(0.1): 1.033 µm		d(0.5):	2.260 µm		d(0.60): 2.65 µm		d(0.9): 4.467 µm



VR004, Tuesday, October 15, 2002 10:57:45 AM

Size (µm)	Vol Under %
0.010	0.00
0.011	0.00
0.013	0.00
0.015	0.00
0.017	0.00
0.020	0.00
0.023	0.00
0.026	0.00
0.030	0.00
0.035	0.00
0.040	0.00
0.046	0.00
0.052	0.00
0.060	0.00
0.069	0.00
0.079	0.00
0.091	0.00

Size (µm)	Vol Under %
0.105	0.00
0.120	0.00
0.138	0.00
0.158	0.00
0.182	0.00
0.209	0.00
0.240	0.00
0.275	0.00
0.316	0.00
0.363	0.00
0.417	0.08
0.479	0.33
0.550	0.05
0.631	1.73
0.724	3.11
0.832	5.16
0.955	7.90

Size (µm)	Vol Under %
1.096	11.70
1.259	16.61
1.445	22.64
1.660	29.63
1.905	37.00
2.188	45.86
2.512	58.29
2.884	65.57
3.311	74.29
3.802	82.00
4.365	88.34
5.012	93.15
5.754	96.40
6.607	98.48
7.586	99.52
8.710	99.92
10.000	100.00

Size (µm)	Vol Under %
11.482	100.00
13.183	100.00
15.136	100.00
17.378	100.00
19.953	100.00
22.909	100.00
26.303	100.00
30.200	100.00
34.674	100.00
39.811	100.00
45.709	100.00
52.481	100.00
60.256	100.00
69.183	100.00
79.433	100.00
91.201	100.00
104.713	100.00

Size (µm)	Vol Under %
120.226	100.00
138.038	100.00
158.489	100.00
181.970	100.00
208.930	100.00
239.883	100.00
275.423	100.00
316.228	100.00
363.078	100.00
416.869	100.00
478.630	100.00
549.541	100.00
630.957	100.00
724.436	100.00
831.764	100.00
954.993	100.00
1096.478	100.00

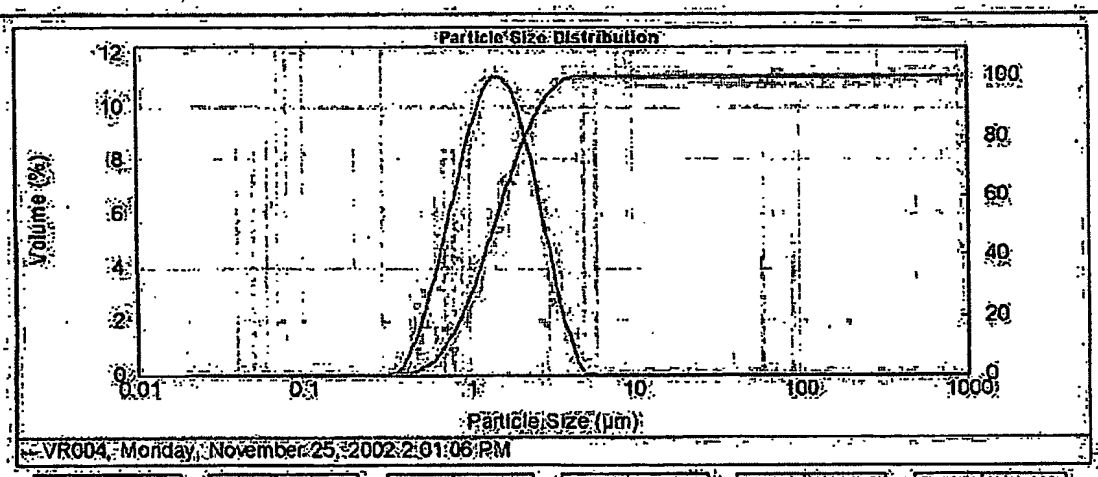
Size (µm)	Vol Under %
1258.925	100.00
1445.440	100.00
1659.587	100.00
1905.461	100.00
2187.762	100.00
2511.886	100.00
2884.032	100.00
3311.311	100.00
3801.894	100.00
4365.158	100.00
5011.872	100.00
5754.399	100.00
6606.934	100.00
7585.776	100.00
8709.636	100.00
10000.000	100.00

Figure 23(a)

MASTERSIZER 2000

Result Analysis Report

Particle Name: VR004		Accessory Name: Hydro 2000SM (A)		Obscuration:	10.59 %
Particle RI: 3.000	Absorption: 0.05	Analysis model: General purpose		Obscuration (blue):	12.66 %
Dispersant: Cyclohexane		Dispersant RI: 1.426		Weighted Residual:	0.774 %
Vol Weighted Mean D[4,3]:	1.623 µm	Mode:	1.517 µm	Specific Surface Area:	4.75 m²/g
Surface Weighted Mean D[3,2]:	1.293 µm	Span:	1.406	Concentration:	0.0016 %Vol
Result units: Volume		Uniformity:	0.436		
d(0.1): 0.727 µm		d(0.5): 1.453 µm		d(0.90): 2.770 µm	



Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %
0.010	0.00	0.105	0.00	1.096	30.53	11.482	100.00	120.226	100.00	1259.853	100.00
0.011	0.00	0.119	0.00	1.239	39.77	13.183	100.00	138.038	100.00	1446.440	100.00
0.013	0.00	0.136	0.00	1.446	49.60	15.136	100.00	158.489	100.00	1659.587	100.00
0.015	0.00	0.156	0.00	1.660	59.07	17.378	100.00	181.970	100.00	1905.461	100.00
0.017	0.00	0.182	0.00	1.905	68.35	19.953	100.00	208.930	100.00	2187.762	100.00
0.020	0.00	0.209	0.00	2.188	76.16	22.909	100.00	239.883	100.00	2511.886	100.00
0.023	0.00	0.240	0.00	2.512	83.00	26.303	100.00	275.423	100.00	2884.032	100.00
0.026	0.00	0.275	0.00	2.884	91.51	30.200	100.00	316.228	100.00	3311.311	100.00
0.030	0.00	0.316	0.00	3.311	93.73	34.674	100.00	363.078	100.00	3801.894	100.00
0.035	0.00	0.363	0.00	3.802	96.22	39.811	100.00	416.869	100.00	4365.158	100.00
0.040	0.00	0.417	0.23	4.365	98.65	45.709	100.00	478.630	100.00	5011.872	100.00
0.046	0.00	0.479	1.10	5.012	99.97	52.481	100.00	549.541	100.00	5754.399	100.00
0.052	0.00	0.550	2.07	5.754	100.00	60.256	100.00	630.957	100.00	6606.934	100.00
0.060	0.00	0.631	3.74	6.607	100.00	69.183	100.00	724.436	100.00	7585.776	100.00
0.069	0.00	0.724	6.68	7.586	100.00	79.433	100.00	831.764	100.00	8709.636	100.00
0.079	0.00	0.832	12.46	8.710	100.00	91.201	100.00	954.993	100.00	10000.000	100.00
0.091	0.00	0.955	22.37	10.000	100.00	104.713	100.00	1096.478	100.00		

Operator notes: Lebbook 27:053

Figure 23(b)

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